República de Colombia
Ministerio de Salud y Protección Social
Instituto Nacional de Vigilancia de Medicamentos y Alimentos – INVIMA

RESOLUCIÓN No. 2021023307 DE 11 de Junio de 2021
Por la cual se concede un Registro Sanitario

La Directora Técnica de Dispositivos Médicos y otras Tecnologías del Instituto Nacional de Vigilancia de Medicamentos y Alimentos INVIMA, en ejercicio de las facultades Legales conferidas en el Decreto 2078 de 2012, Decreto Reglamentario 3770 de 2004, Ley 1437 de 2011 y Ley 962 de 2005.

CONSIDERANDO

QUE ANTE ESTE INSTITUTO SE HA SOLICITADO LA CONCESIÓN DE UN REGISTRO SANITARIO AUTOMATICO EN CUMPLIMIENTO A LA VERIFICACIÓN DE LA DOCUMENTACIÓN TÉCNICO LEGAL ALLEGADA ANTE LA DIRECCIÓN DE DISPOSITIVOS MÉDICOS Y OTRAS TECNOLOGÍAS, EMITIENDO CONCEPTO FAVORABLE PARA LA EXPEDICIÓN DE ESTE REGISTRO SANITARIO.
EN CONSECUENCIA A LO ANTERIOR, DE CONFORMIDAD CON EL ARTICULO 57 DE LA LEY 962 DE 2005 EL INVIMA REALIZARA EL CONTROL POSTERIOR DENTRO DE LOS QUINCE (15) DIAS SIGUIENTES A SU EJECUTORIA.

RESUELVE

ARTICULO PRIMERO.- CONCEDER REGISTRO SANITARIO POR EL TÉRMINO DE DIEZ (10) AÑOS A

NOMBRE DEL REACTIVO	PRESENTACIÓN, COMPONENTES DEL KIT Y REFERENCIA (S)
1. VIDAS NEPHROCHECK (NEPH)	Kit para 30 o 60 pruebas: Cartuchos (NEPH) STR / Tiras (NEPH) STR Conos SPR (NEPH) Calibrador S1 (NEPH) Control C1 (NEPH)
TOTAL DE REACTIVOS	1

REGISTRO SANITARIO NO.:	**INVIMA 2021RD-0006933**
MODALIDAD:	IMPORTAR Y VENDER
TITULAR(ES):	BIOMERIEUX S.A CON DOMICILIO EN FRANCIA
FABRICANTE(S):	BIOMERIEUX S.A CON DOMICILIO EN FRANCIA
IMPORTADOR(ES):	BIOMERIEUX COLOMBIA S.A.S CON DOMICILIO EN BOGOTA - D.C.
ACONDICIONADOR(ES):	SUPPLA S.A. CON DOMICILIO EN BOGOTA - D.C.
CATEGORÍA:	II
ÁREA:	INMUNOLOGÍA
USO:	DETERMINACIÓN DE LOS DIFERENTES ANALITOS RELACIONADOS CON MUESTRAS PROCEDENTES DEL ORGANISMO HUMANO
EXPEDIENTE NO.:	20204170
RADICACIÓN NO.:	20211111783
FECHA DE RADICACIÓN. :	09/06/2021

ARTICULO SEGUNDO.- SE APRUEBAN LAS ETIQUETAS APORTADAS EN LA SOLICITUD DEL REGISTRO SANITARIO.

ARTICULO TERCERO.-CONTRA LA PRESENTE RESOLUCIÓN PROCEDE ÚNICAMENTE EL RECURSO DE REPOSICIÓN, QUE DEBERÁ INTERPONERSE ANTE LA DIRECIÓN DE DISPOSITIVOS MÉDICOS Y OTRAS TECNOLOGÍAS DE INVIMA, DENTRO DE LOS DIEZ (10) DÍAS SIGUIENTES A SU NOTIFICACIÓN, EN LOS TÉRMINOS SEÑALADOS EN EL CÓDIGO DE PROCEDIMIENTO ADMINISTRATIVO Y DE LO CONTENCIOSO ADMINISTRATIVO.

ARTICULO CUARTO.- LA PRESENTE RESOLUCIÓN RIGE A PARTIR DE LA FECHA DE SU EJECUTORIA.

Instituto Nacional de Vigilancia de Medicamentos y Alimentos - Invima
Oficina Principal: Cra 10 N° 64 - 28 - Bogotá
Administrativo: Cra 10 N° 64 - 60
(1) 2948700
www.invima.gov.co

República de Colombia
Ministerio de Salud y Protección Social
Instituto Nacional de Vigilancia de Medicamentos y Alimentos – INVIMA

RESOLUCIÓN No. 2021023307 DE 11 de Junio de 2021
Por la cual se concede un Registro Sanitario

La Directora Técnica de Dispositivos Médicos y otras Tecnologías del Instituto Nacional de Vigilancia de Medicamentos y Alimentos INVIMA, en ejercicio de las facultades Legales conferidas en el Decreto 2078 de 2012, Decreto Reglamentario 3770 de 2004, Ley 1437 de 2011 y Ley 962 de 2005.

ARTICULO QUINTO.- LOS DERECHOS QUE SE DERIVEN DE ESTA RESOLUCIÓN QUEDARAN SUJETAS AL CONTROL POSTERIOR QUE DEBE REALIZAR EL INSTITUTO NACIONAL DE VIGILANCIA DE MEDICAMENTOS Y ALIMENTOS INVIMA DE CONFORMIDAD CON LO PREVISTO POR EL ARTICULO 13 DEL DECRETO 3770 DE 2004.

COMUNIQUESE, NOTIFIQUESE Y CUMPLASE

DADA EN BOGOTÁ D.C. A LOS 11 DE JUNIO DE 2021
ESTE ESPACIO, HASTA LA FIRMA SE CONSIDERA EN BLANCO.

LUCIA AYALA RODRIGUEZ
DIRECTORA TECNICA DE DISPOSITIVOS MEDICOS Y OTRAS TECNOLOGIAS
PROYECTO: LEGAL: FMOSCOSOM, TÉCNICO: JROMEROM, REVISÓ:CORDINA_VARIOSJPACHECO

Signature Not Verified
Firmado digitalmente por LUCIA AYALA RODRIGUEZ
Fecha: 2021/06/15 10:09:09 COT
Razón: Invima
Locación: BOGOTA D.C., Colombia

Instituto Nacional de Vigilancia de Medicamentos y Alimentos - Invima
Oficina Principal: Cra 10 N° 64 - 28 - Bogotá
Administrativo: Cra 10 N° 64 - 60
(1) 2948700
www.invima.gov.co

BIOMÉRIEUX

REF 421172 / 421172-03

054303 - 02 - 2022-03

ES

VIDAS® NEPHROCHECK® (NEPH)

IVD

Uso previsto

VIDAS® NEPHROCHECK® es una prueba automatizada para utilizar en el instrumento VIDAS® 3 para la determinación cuantitativa inmunoenzimática de las proteínas TIMP-2 (Inhibidor tisular de metaloproteinasa-2) e IGFBP-7 (Proteína de unión al factor de crecimiento similar a la insulina 7) en la orina humana mediante la técnica ELFA (Ensayo de fluorescencia ligado a enzima).

El test VIDAS® NEPHROCHECK® está diseñado para utilizarse junto con evaluación clínica para prestar ayuda al análisis de riesgo de la lesión renal aguda (LRA (AKI)) moderada o grave en pacientes agudos.

Resumen y explicación

La proteína de unión al factor de crecimiento similar a la insulina 7 (IGFBP-7) es una proteína soluble de aproximadamente 26 kilodalton (kDa) de peso molecular que se encuentra en los riñones y en otros tejidos.[1] Se cree que la IGFBP-7 está involucrada o inducida en varios tipos de procesos que se han asociado con lesiones celulares.[2-8]

El inhibidor tisular de metaloproteinasa-2 (TIMP-2) es una proteína soluble de aproximadamente 22 kDa de peso molecular que se encuentra en los riñones y en otros tejidos.[9] El TIMP-2 se une e inhibe la actividad de varias metaloproteinasas (MMP).[10] El TIMP-2 también activa a la MMP2. A través de su actividad en las MMP, se cree que el TIMP-2 está involucrado o inducido en varios procesos asociados con la infiltración de leucocitos, las lesiones celulares y la ruptura de los contactos celulares.[11-16]

El TIMP-2 y la IGFBP-7 también están implicados en el fenómeno de la parada del ciclo celular G1 durante las primeras fases de la lesión celular.[17-20]

La LRA involucra a una serie de vías moleculares y celulares extremadamente complejas que implican a las células endoteliales, epiteliales, inflamatorias e intersticiales. Estos mecanismos incluyen las vías del ciclo celular, de inmunidad, de inflamación y de apoptosis.

Recientemente, se ha demostrado que, al igual que ocurre con otras células epiteliales, las células tubulares renales entran en un pequeño periodo de parada del ciclo celular G1 tras la lesión por sepsis o isquemia experimental.[2,21] Se cree que esto evita que las células se dividan cuando el ADN puede estar dañado y que para el proceso de la división celular hasta que el daño se pueda reparar para que no provoque muerte o senectud celular.[18]

También se sabe que el TIMP-2 y la IGFBP-7 están involucrados en la respuesta a una amplia variedad de agresiones (inflamación, agresión oxidativa, radiación ultravioleta, fármacos y toxinas).[19,20,22] Esto puede ayudar a explicar por qué corresponden al riesgo de LRA.

Ya se han publicado estudios de evaluación de la combinación de TIMP-2 y IGFBP-7 para el análisis del riesgo del LRA humano. En una publicación, se realizaron dos estudios observacionales multicéntricos en los pacientes de interés.[23] El primer estudio involucró a 522 adultos de tres cohortes diferentes (incluidos pacientes con sepsis, choques, cirugías mayores y traumatismos) y examinó alrededor de 300 posibles marcadores de LRA. El segundo estudio involucró a 744 sujetos adultos con enfermedades graves y sin pruebas de LRA al inicio del estudio. La cohorte del análisis final consistió en una muestra heterogénea de 728 pacientes de interés. El criterio principal de valoración fue una LRA moderada o grave en un plazo de 12 horas tras la obtención de la muestra. El estudio mostró que la IGFBP-7 y el TIMP-2 urinarios en combinación obtuvieron un área bajo la curva de 0,80. Además, [TIMP-2]x[IGFBP-7] aumentó de forma significativa la estratificación del riesgo al añadirse a un modelo clínico de nueve variables y al analizarse mediante el modelo de riesgos instantáneos proporcionales de Cox, la ecuación de estimación generalizada, la mejora de la discriminación integrada o la mejora de la reclasificación neta.

La LRA es una de las enfermedades más graves y prevalentes en los pacientes hospitalizados y está asociada con una gran cantidad de enfermedades crónicas y agudas.[24-29] La carga económica y sanitaria de la LRA es abrumadora, ya que presenta un aumento importante de la mortalidad y morbilidad, así como de la duración de la estancia en la unidad de cuidados intensivos y de los costes de hospitalización, además de consecuencias para la salud a largo plazo.[30-36]

Las pruebas para evaluar la LRA en pacientes agudos proporcionan información importante a los médicos y, junto con otra información clínica disponible, pueden ayudar a los médicos a optimizar el tratamiento del paciente.[27,36-38]

Por pacientes agudos se entienden las personas en las que la enfermedad ha aparecido de forma abrupta y progresa con rapidez, lo que hace que necesiten asistencia urgente.

Principio

El principio de la determinación combina un método inmunoenzimático de tipo sándwich en una etapa con una detección final por fluorescencia (ELFA).

El SPR (Solid Phase Receptacle, o recipiente de fase sólida) sirve a la vez de fase sólida y de dispositivo de pipeteo. Los reactivos del test están listos para ser utilizados y previamente distribuidos en los cartuchos de reactivos de un solo uso sellados.

El instrumento realiza automáticamente todos los pasos del test.

La muestra se transfiere a los pocillos que contienen anticuerpos anti-IGFBP-7 y anti-TIMP-2 marcados con fosfatasa alcalina (conjugado). La mezcla de la muestra/conjugado se somete a una sucesión de ciclos de aspiración/expulsión en el cono SPR. Esta operación permite que las dos proteínas se fijen a la inmunoglobulina que recubre la pared interior del cono SPR y el conjugado hasta formar un sándwich.

Los componentes no fijados se eliminan durante las etapas de lavado.

Las dos etapas de detección se realizan sucesivamente. Durante cada paso de detección, el sustrato (4-metilumbeliferil fosfato) se aspira y expulsa del cono SPR. La enzima del conjugado cataliza la reacción de hidrólisis de este substrato en un producto fluorescente (4-metil-umbeliferona) cuya fluorescencia se mide a 450 nm.

Para cada proteína, la intensidad de la fluorescencia es proporcional a la concentración de la muestra. Al final del estudio, el instrumento calcula las concentraciones de proteínas en relación con las dos curvas de calibración, una para cada proteína, codificadas en los datos MLE (introducción del lote maestro).

A continuación, el instrumento calcula la puntuación AKIRISK™ de forma automática como el producto de las concentraciones de los dos biomarcadores, en ng/mL, dividido entre 1000, conforme a la siguiente fórmula:

Puntuación AKIRISK™ = (TIMP-2 x IGFBP-7)/1000.

Después, los resultados pueden imprimirse.

Contenido del kit - 60 PRUEBAS o 30 PRUEBAS

Nota: El test VIDAS® NEPHROCHECK® está disponible en kits de 60 pruebas (REF 421172) o en kits de 30 pruebas (REF 421172-03), en función del país. Póngase en contacto con su representante local para obtener más información.

REF 421172: 60 cartuchos[a] (NEPH)	STR	Listo al empleo.
REF 421172-03: 30 tiras[a] (NEPH)		
REF 421172: 60 dispositivos SPR(NEPH) 2 x 30	SPR	Listo al empleo. El interior de los conos SPR está recubierto de: anticuerpo IgG monoclonal murino anti-IGFBP-7 y anti-TIMP-2 + estabilizador de origen animal + conservante.
REF 421172-03: 30 dispositivos SPR(NEPH) 1 x 30		
Calibrador S1[b] (NEPH) 1 x 1,6 mL (líquido)	S1	Listo al empleo. Tampón con proteínas + estabilizador de origen animal + conservante. Para cada proteína, los datos MLE (Introducción del lote patrón) indican el intervalo aceptable en “Valor de fluorescencia relativa” [“Intervalo de RFV del calibrador (S1)”].

Control C1[b] (NEPH) 1 x 1,2 mL (líquido)	C1	Listo al empleo. Tampón con proteínas + estabilizador de origen animal + conservante. Los datos de MLE indican el intervalo aceptable para la puntuación AKIRISK™ [“Intervalo de valor de puntuación de control (C1)”].
Especificaciones de los datos de calibración de fábrica necesarios para la calibración del test: Código de barras MLE impreso en la etiqueta del envase.		
1 ficha técnica disponible para descargar en www.biomerieux.com		


[a] **PELIGRO** **ATENCIÓN** H290 / H315 / H317 / H318 / H319 / H335 / EUH208 / P261 / P280 / P302 + P352 / P305 + P351 + P338

[b] **ATENCIÓN** H317 / EUH208 / P261 / P280 / P302 + P352

Indicaciones de peligro
- H290: Puede ser corrosivo para los metales.
- H315: Provoca irritación cutánea.
- H317: Puede provocar una reacción alérgica en la piel.
- H318: Provoca lesiones oculares graves.
- H319: Provoca irritación ocular grave.
- H335: Puede irritar las vías respiratorias.
- EUH208: Contiene 2-metil-2H-isotiazolin-3-ona. Puede provocar una reacción alérgica.

Indicaciones de precaución
- P261: Evitar respirar el polvo/el humo/el gas/la niebla/los vapores/el aerosol.
- P280: Llevar guantes/prendas/gafas/máscara de protección.
- P302 + P352: EN CASO DE CONTACTO CON LA PIEL: Lavar con agua y jabón abundantes.
- P305 + P351 + P338: EN CASO DE CONTACTO CON LOS OJOS: Aclarar cuidadosamente con agua durante varios minutos. Quitar las lentes de contacto, si lleva y resulta fácil. Seguir aclarando.

Para obtener más información, consulte la ficha de datos de seguridad.

El cono SPR
El interior del cono SPR está recubierto durante la producción con anticuerpos monoclonales anti-IGFBP-7 y anti-TIMP-2 (murinos). Cada cono SPR está identificado con el código “NEPH”. Extraiga únicamente el número necesario de conos SPR de la bolsita y séllela de nuevo con cuidado después de abrirla.

El cartucho de reactivos
El cartucho está compuesto por 10 pocillos recubiertos de una hoja de aluminio sellada y etiquetada. En la etiqueta hay un código de barras que indica principalmente el código de la prueba, el número de lote y la fecha de caducidad de la caja.La hoja de aluminio del primer pocillo está perforada para facilitar la introducción de la muestra. El último pocillo de cada cartucho es una cubeta en la cual se realiza la lectura fluorométrica. Los pocillos de la sección central del cartucho contienen varios reactivos necesarios para el test.

Descripción del cartucho VIDAS® NEPHROCHECK® (NEPH)
El cartucho contiene dietanolamina y acida sódica. Consulte las indicaciones de peligro “H” y las indicaciones de precaución “P” arriba indicadas.[a]

Pocillos	Reactivos
1	Pocillo para la muestra: dispense 100 µL de calibrador, control o muestra.
2	Conjugado: tampón con IgG monoclonal anti-IGFBP-7 marcado con fosfatasa alcalina (murino) + IgG monoclonal anti-TIMP-2 marcado con fosfatasa alcalina (de conejo) + estabilizador de origen animal + conservante.
3	Tampón de lavado con conservante.

Pocillos	Reactivos
4	Pocillo vacío.
5	Tampón de lavado ácido.
6-7-8	Tampón de lavado con conservante.
9	Sustrato: 4-metilumbeliferil fosfato (0,6 mmol/L) + conservante.
10	Cubeta de lectura con sustrato: 4-metilumbeliferil fosfato (0,6 mmol/L) + conservante.

Materiales y productos desechables necesarios pero no suministrados

- Pipetas y/o micropipetas de un solo uso para dispensar los volúmenes adecuados.
- Guantes desechables sin talco.
- Para obtener más información sobre otros materiales y productos desechables específicos, consultar el Manual de usuario del instrumento.
- Instrumento de la familia VIDAS®: VIDAS® 3 con la versión 1.3.2 como mínimo o con una versión superior.

Precauciones de utilización

- **Únicamente para diagnóstico *in vitro*.**
- **Exclusivamente para uso profesional por parte de personal de laboratorio cualificado en laboratorios clínicos.**
- Este kit no contiene productos de origen humano.
- Este equipo contiene compuestos de origen animal. El origen y/o el estado sanitario de los animales no pueden garantizar de forma absoluta que estos productos no contienen ningún agente patógeno transmisible; se recomienda manipularlos con las precauciones de uso relativas a los productos potencialmente infecciosos (no ingerir; no inhalar).
- No utilice los conos SPR si la bolsita está perforada o si la pegatina de sellado de un cono SPR se ha despegado.
- No utilice cartuchos visiblemente deteriorados (hoja de aluminio o plástico dañados).
- No utilizar los reactivos después de su fecha de caducidad indicada en la etiqueta del envase.
- No mezclar reactivos (o productos desechables) de lotes diferentes.
- Los reactivos del test VIDAS® NEPHROCHECK® solo se deben utilizar con el instrumento VIDAS® 3.
- Usar guantes sin talco, ya que se ha documentado que el talco provoca falsos resultados para determinadas pruebas inmunoenzimáticas.
- Los reactivos del kit contienen un conservante (azida sódica) susceptible de reaccionar con las tuberías de plomo o de cobre, formando nitruros metálicos explosivos. Si se tira por el desagüe algún líquido que contiene nitruro sódico, las tuberías deben lavarse con agua para evitar su acumulación.
- Consulte las indicaciones de peligro “H” y las indicaciones de precaución “P” arriba indicadas.
- Los derrames que se produzcan deben limpiarse cuidadosamente después del tratamiento con detergente líquido o una solución de lejía doméstica que contenga como mínimo un 0,5% de hipoclorito sódico. Consultar el Manual de usuario para limpiar los derrames producidos sobre o en el interior del instrumento. No someter a autoclave soluciones que contengan lejía.
- Deben realizarse tareas de limpieza y descontaminación en el instrumento con regularidad (consulte el Manual de usuario para conocer las operaciones de mantenimiento preventivo y por parte del usuario).

Condiciones de almacenamiento

- Almacenar el kit a +2 °C/+8 °C.
- No congelar los reactivos.
- **Almacene todos los reactivos no utilizados a +2 °C/+8 °C.**
- Tras abrir el kit, comprobar que las bolsas de los conos SPR estén cerradas correctamente e intactas. De lo contrario, no utilice los conos SPR.
- **Después del uso, vuelva a sellar con cuidado la bolsita con el desecante en el interior para mantener la estabilidad de los conos SPR y conserve todo el kit a +2 °C/+8 °C.**
- Si se conservan en las condiciones recomendadas, todos los componentes son estables hasta la fecha de caducidad indicada en la etiqueta del envase, a excepción de los conos SPR, que se mantienen estables durante

10 meses a una temperatura de +2 °C/+8 °C tras su apertura. Consulte la tabla de composición del kit para ver las condiciones especiales de conservación.

Muestras

Naturaleza y toma de muestras

Orina (reciente o congelada).

Tipos de tubos validados

- Tubo de plástico sin aditivos.

Puesto que algunos tubos de muestras pueden contener substancias susceptibles de producir interferencias en los resultados de esta prueba, se aconseja validarlos antes de usarlos.

Cada laboratorio es responsable de validar el tipo de tubo de muestra empleado, así como de seguir las recomendaciones de uso del fabricante.

Preparación de la muestra reciente

El documento WHO/DIL/LAB/99.1 actual incluye recomendaciones para la preparación de las muestras. [39]

Seguir las recomendaciones de uso del fabricante del tubo antes de usar tubos de muestras.

1. Recoja una muestra de orina reciente de aproximadamente 10 mL en un recipiente de recogida de muestras limpio sin aditivos. Para los pacientes con sondas vesicales permanentes, primero se debe vaciar la bolsa colectora y, a continuación, se debe recoger una muestra reciente de orina.
2. Las muestras de orina se deben centrifugar en un plazo de una hora tras la obtención de la muestra. Si se recoge la muestra de orina en un recipiente de recogida, invierta el contenedor 3 veces para mezclar la muestra exhaustivamente y, a continuación, transfiera la muestra de orina desde el recipiente de recogida de muestras a un tubo para centrifugadora limpio. Centrifugue la muestra de orina durante 10 minutos a 1000 x g a +2 °C/+25 °C.
3. Una vez que haya centrifugado la muestra, transfiera el sobrenadante a un tubo limpio.
4. Compruebe el sobrenadante en un plazo de 5 horas tras la obtención de la muestra. Si necesita almacenar el sobrenadante durante más de 5 horas, transfiéralo a un tubo de proteína de baja unión.
5. Si la prueba se realiza en un plazo de 24 horas, la muestra se debe almacenar a +2 °C/+8 °C.
6. Si se necesita almacenar la muestra durante más de 24 horas, realice una congelación rápida de la muestra en un plazo de 5 horas tras la obtención de la muestra y almacénela a ≤ −60 °C.

Preparación de muestras congeladas o refrigeradas

Para analizar una muestra congelada o refrigerada, descongele y caliente la muestra de orina a temperatura ambiente (+18 °C/+25 °C), pero no más de 60 minutos. Asegúrese de haber descongelado o calentado debidamente la muestra. Después de descongelarla, como puede que haya precipitados en el tubo de muestra, inviértalo con cuidado como mínimo 3 veces para homogeneizar la muestra. No utilice un agitador tipo vórtex. Asegúrese de que la muestra esté bien homogeneizada antes de analizarla para así tener la garantía de que los resultados sean precisos. **Analícela justo después de homogeneizarla.**

Estabilidad de la muestra

Las muestras recientes almacenadas en tubos primarios cerrados se mantienen estables a +18 °C/+25 °C durante hasta 5 horas. Las muestras recientes almacenadas en tubos de proteínas de baja unión se mantienen estables a +2 °C/+8 °C hasta 24 horas.

Las muestras congeladas se mantienen estables a ≤ −60 °C hasta 6 meses, incluyendo dos ciclos de congelación/descongelación.

No almacene las muestras congeladas a temperaturas por encima de −60 °C.

Dilución de la muestra

No diluya las muestras antes de utilizar el test VIDAS® NEPHROCHECK®.

Interferencias relacionadas con la muestra

Es aconsejable no utilizar muestras turbias y, si es posible, extraer una muestra nueva.

Consultar los compuestos analizados en la sección **RESULTADOS - Estudio de interferencias farmacológicas y otras sustancias con capacidad interferente**.

Instrucciones de uso

Consultar las instrucciones completas en el Manual de usuario del instrumento.

Lectura de los datos del protocolo VIDAS® PTC (Protocol Test Change) y de los datos MLE
Cuando utilice por primera vez el test

Con el lector de códigos de barras externo del instrumento, **leer los códigos de barras (PTC y MLE) en el orden siguiente**:

1. Escanee el código o los códigos de barras PTC, que puede descargar de www.biomerieux.com. Esta lectura permite transferir los datos del protocolo VIDAS® PTC al software del instrumento para su actualización.
2. Escanear los datos de la tarjeta MLE situados en la etiqueta del envase.

Cuando se abre un nuevo lote de reactivos

Antes de realizar la prueba, escanear los datos MLE de la etiqueta del envase con el lector de códigos de barras externo del instrumento.

Nota: Los datos de lote patrón de calibración solo deben introducirse una vez para cada lote.

Es posible introducir los datos de MLE **manualmente o de forma automática** según el instrumento (consultar el Manual de usuario).

Calibración
La calibración, que se realiza mediante el calibrador incluido en el kit, debe efectuarse cada vez que se abra un nuevo lote de reactivos, tras introducir los datos MLE y, después, cada **56 días**. Esta operación ofrece curvas de calibración específicas para cada instrumento y compensa las posibles variaciones menores en la señal de la prueba durante toda la vida útil del kit.

El calibrador, identificado como S1, se debe analizar por duplicado. Para cada proteína, el valor del calibrador debe estar comprendido en el intervalo de RFV (Valor de fluorescencia relativa) establecido. En caso contrario, se debe calibrar de nuevo mediante el S1.

Controles del kit
En cada kit VIDAS® NEPHROCHECK® se incluye un control. Este control debe procesarse inmediatamente al abrir un nuevo kit con el fin de asegurar que el rendimiento de los reactivos no ha está alterado. También es necesario comprobar cada calibración mediante el uso de este control. Para que el instrumento pueda verificar el valor del control, es preciso identificarlo como C1.

No se podrán validar los resultados si el valor del control se desvía de los valores previstos.

Nota: El objetivo del control del kit es validar la calibración. Cualquier otro uso del control del kit queda bajo la responsabilidad del cliente.

Procedimiento

1. **Extraer del refrigerador el kit conservado a +2 °C/+8 °C y sacar los reactivos necesarios. Después de cada utilización, vuelva a sellar correctamente la bolsa y vuelva a guardar el kit completo a 2-8 °C.** Los reactivos pueden usarse inmediatamente.
2. Utilice un cartucho “NEPH” y un cono SPR “NEPH” para cada muestra, control o calibrador que se vaya a analizar. Compruebe que la bolsita de SPR haya quedado bien sellada después de retirar los dispositivos SPR necesarios.
3. La prueba se identifica mediante el código “NEPH” en el instrumento. El calibrador, identificado como S1, se debe analizar por duplicado. El control, identificado como C1, se debe analizar una sola vez.
4. Mezcle el calibrador y el control con un agitador tipo vórtex o invierta los viales por lo menos 3 veces.
5. **No mezcle las muestras con un agitador tipo vórtex. Para obtener unos resultados óptimos, consulte todos los párrafos de la sección MUESTRAS.**
6. Antes de pipetear, comprobar que no hay burbujas en las muestras.
7. El volumen necesario de calibrador, controles y muestras para esta prueba es de 100 µL.
8. Inserte los conos SPR “NEPH” y los cartuchos “NEPH” en el instrumento. Asegúrese de que las etiquetas de color con el código de la prueba que se incluyen en los dispositivos SPR y los cartuchos coinciden.
9. Iniciar el test como se indica en el Manual de usuario. El instrumento lleva a cabo todas las etapas del test de forma automática.
10. Cierre los viales y colóquelos a la temperatura adecuada tras pipetear.
11. La duración de la prueba es de **aproximadamente 46 minutos.** Cuando el ensayo haya finalizado, retire los dispositivos SPR y los cartuchos del instrumento.
12. Elimine los conos SPR y cartuchos usados en un recipiente apropiado.

Control de calidad

Es posible realizar controles de calidad adicionales conforme a las normas locales o los requisitos de acreditación, así como conforme a los requisitos definidos en el procedimiento de control de calidad del laboratorio.

Resultados e interpretación

Una vez finalizado el test, el ordenador analiza automáticamente los resultados. Para cada proteína, se realizan dos mediciones de fluorescencia en la cubeta de lectura de los cartuchos de reactivos con cada una de las muestras. La primera lectura es una lectura del ruido de fondo de la cubeta con sustrato antes de la introducción del SPR en el sustrato.

La segunda lectura se efectúa tras la incubación del sustrato con la enzima que puede estar unida al interior del dispositivo SPR. El RFV (Relative Fluorescence Value; es decir, valor de fluorescencia relativo) se calcula restando la fluorescencia inicial del resultado final. Este cálculo aparece en la hoja de resultados.

El instrumento calcula las concentraciones de las dos proteínas de forma automática mediante las curvas de calibración que almacena el instrumento (modelo logístico de 4 parámetros).

El instrumento calcula la puntuación AKIRISK™ como el producto de las concentraciones medidas de las dos proteínas, TIMP-2 y IGFBP-7, medidas en ng/mL, divididas por 1000: puntuación de AKIRISK™= ([TIMP-2] x [IGFBP-7])/1000 (unidades = $(ng/mL)^2/1000$).

La puntuación AKIRISK™ se muestra en el instrumento una vez que el procedimiento de la determinación haya finalizado. No se muestran las concentraciones de las proteínas individuales. La puntuación AKIRISK™ se muestra sin unidades.

Trazabilidad metrológica
La calibración del test VIDAS® NEPHROCHECK® se puede contrastar con los calibradores de referencia del hospital para cada una de las dos proteínas.

Umbral e interpretación de los resultados
Se han establecido dos límites para la puntuación AKIRISK™, uno de 0,30 y otro de 2,00, en función de los resultados de los estudios clínicos anteriores.[40]

La puntuación AKIRISK™ que muestra el instrumento se debe interpretar según lo descrito en la siguiente tabla.

Puntuación AKIRISK™	Interpretación
≤ 0,30	El paciente tiene un **riesgo menor** de desarrollar una LRA moderada o grave en un plazo de 12 horas tras la evaluación que los pacientes de interés con puntuaciones AKIRISK™ > 0,30
> 0,30	El paciente presenta un **aumento del riesgo** de desarrollar una LRA moderada o grave en un plazo de 12 horas tras la evaluación en relación con los pacientes de interés con puntuaciones AKIRISK™ ≤ 0,30
> 2,00	El paciente presenta un **riesgo mayor** de desarrollar una LRA moderada o grave en un plazo de 12 horas tras la evaluación en relación con los pacientes de interés con puntuaciones AKIRISK™ ≤ 0,30

Límites de la prueba

1. Pueden existir interferencias con determinadas muestras que contengan anticuerpos dirigidos contra los componentes del reactivo. Por este motivo, se deben interpretar los resultados del test teniendo en cuenta la historia clínica del paciente, así como los resultados de otras pruebas que se hayan realizado.
2. Los resultados que no concuerden con la historia clínica del paciente pueden deberse a un mantenimiento inadecuado del instrumento (consulte el Manual de usuario del instrumento).

Intervalos de referencia

Estos resultados se dan a título indicativo. Se recomienda que cada laboratorio establezca sus propios intervalos de referencia sobre una población rigurosamente seleccionada.

Se realizó un estudio del intervalo de referencia de acuerdo con las recomendaciones del documento EP28-A3c del CLSI.[41]

Los intervalos de referencia se determinaron de forma independiente en dos cohortes de pacientes adultos, sujetos aparentemente sanos (N=378) y sujetos con enfermedades crónicas estables (sin enfermedades agudas) (N=372).

Los intervalos de referencia se definieron según el 95 % central de la distribución de las puntuaciones AKIRISK™, es decir, según los percentiles de 2,5 y 97,5. Los resultados se muestran en la tabla que figura a continuación.

Intervalos de referencia para sujetos aparentemente sanos y sujetos con enfermedades crónicas estables

Cohorte	Género	Número de sujetos	Intervalo de puntuación AKIRISK™
Sujetos aparentemente sanos	Mujer	191	[< 0,04-2,81]
	Hombre	187	[< 0,04-3,06]
	Todos	378	[< 0,04-2,50]
Sujetos con enfermedades crónicas estables	Mujer	191	[< 0,04-2,91]
	Hombre	181	[< 0,04-2,63]
	Todos	372	[< 0,04-2,66]

El intervalo de referencia general para los sujetos sanos en apariencia fue de < 0,04 a 2,50. El intervalo de referencia general para los sujetos con enfermedades crónicas estables fue de < 0,04 a 2,66. Los intervalos de referencia eran comparables para sujetos aparentemente sanos y sujetos con enfermedades crónicas estables, así como para hombres y mujeres.

En la tabla que figura a continuación, se muestra información demográfica y de otro tipo acerca de las dos cohortes.

Características demográficas de los sujetos aparentemente sanos y de los sujetos con enfermedades crónicas estables

Características demográficas		Cohorte de sujetos aparentemente sanos N total = 378		Cohorte de sujetos con enfermedades crónicas estables N total = 372	
		N, media o mediana	%, DE o IQR	N, media o mediana	%, DE o IQR
Edad (años)	Media (DE)*	54,1	(17,3)	62,7	(14,7)
	Mediana (IQR)**	56,0	(40,0-68,0)	65,0	(53,0-75,0)
IMC (kg/m^2)	Media (DE)*	27,5	(5,9)	30,8	(7,0)
	Mediana (IQR)**	26,8	(23,3-29,8)	29,8	(26,2-34,5)
Sexo	Mujer	191	(50,5)	191	(51,3)
	Hombre	187	(49,5)	181	(48,7)

*DE: Desviación estándar

**IQR: Rango intercuartílico (50 % central)

Prestaciones

Los estudios realizados con el test VIDAS® NEPHROCHECK® han proporcionado los siguientes resultados:

Intervalo de medición analítica (IMA)

El intervalo de medición analítica (IMA) es el intervalo de valores correspondiente a los límites de rendimiento aceptables (precisión y linealidad).

El IMA para IGFBP-7 es [20-400] ng/mL.

El IMA para TIMP-2 es [2-25] ng/mL.

El instrumento muestra la puntuación AKIRISK™ de 0,04 a 10,00.

Para calcular la puntuación AKIRISK™, si alguna de las dos concentraciones de proteínas individuales está por debajo del IMA, la concentración de proteínas se establecerá en el límite más bajo del IMA (2 ng/mL para TIMP-2 y 20 ng/mL para IGFBP-7) antes de calcular la puntuación AKIRISK™.

Del mismo modo, si alguna de las dos concentraciones de proteínas individuales está por encima del IMA, la concentración de proteínas se establecerá en el límite más alto del IMA (25 ng/mL para TIMP-2 y 400 ng/mL para IGFBP-7) antes de calcular la puntuación AKIRISK™.

Linealidad

Se evaluaron las proteínas TIMP-2 y IGFBP-7 utilizadas para obtener la puntuación AKIRISK™ y se demostró que son lineales en el intervalo de medición de la puntuación AKIRISK™. Sin embargo, no se espera que la puntuación AKIRISK™ en sí misma sea lineal. La linealidad se evaluó conforme a las recomendaciones del documento EP06-A del CLSI.

Límites de detección

	TIMP-2	IGFBP-7	Puntuación AKIRISK™
Límite de blanco (LoB)	0,286 ng/mL	6,168 ng/mL	0,002
Límite de detección (LoD)	0,359 ng/mL	8,602 ng/mL	0,003
Límite de cuantificación (LoQ)	0,359 ng/mL	8,602 ng/mL	0,003

Los valores LoB, LoD y LoQ se determinaron para cada una de las proteínas TIMP-2 e IGFBP-7 conforme a las recomendaciones del documento EP17-A2 del CLSI. Los valores LoB, LoD y LoQ de la puntuación AKIRISK™ se han obtenido a partir de los valores de ambas proteínas.

El límite del blanco (LoB) es la concentración por debajo de la cual se encuentran el 95% de las muestras sin analitos.

El límite de detección (LoD) es la concentración de analito mínima de una muestra que puede distinguirse de la muestra sin analitos con una probabilidad del 95% (el resultado observado es mayor que el LoB con una probabilidad del 95%).

El límite de cuantificación (LoQ) es la concentración más baja de analito que se puede detectar y medir con un nivel aceptable de precisión. En lo que respecta al ensayo VIDAS® NEPHROCHECK®, el nivel aceptable de precisión se corresponde con una precisión dentro del lote fijada en el 20 % del CV de cada una de las proteínas TIMP-2 e IGFBP-7.

Precisión

Se ha realizado un estudio de precisión de acuerdo con las recomendaciones del documento EP05–A3 del CLSI.[42]

Se ha analizado una serie de muestras humanas que representaban ocho niveles de la puntuación AKIRISK™ en el intervalo de valoración analítica con el instrumento VIDAS® 3. Se han analizado las siguientes fuentes de variabilidad: repetibilidad, análisis, día, calibración y lote.

Se ha calculado, para cada muestra, la repetibilidad (precisión durante el análisis), la precisión dentro del lote y la precisión del laboratorio (entre lotes y entre instrumentos).

La tabla siguiente contiene, a modo de ejemplo, los valores obtenidos con el instrumento VIDAS® 3.

Muestra	N	Media	Repetibilidad (Precisión intraanálisis)		Precisión intralote		Precisión intralaboratorio (entre lotes y entre instrumentos)	
			Desviación estándar	CV (%)*	Desviación estándar	CV (%)*	Desviación estándar	CV (%)*
Muestra 1	96	0,05	0,00	7,8	0,00	9,8	0,01	10,5
Muestra 2	96	0,06	0,01	16,0	0,01	16,2	0,01	16,3
Muestra 3	96	0,19	0,01	5,7	0,01	7,9	0,01	7,9
Muestra 4	96	0,23	0,01	6,4	0,02	7,5	0,02	7,5
Muestra 5	96	0,72	0,04	6,1	0,05	6,7	0,05	6,9
Muestra 6	96	1,70	0,08	4,5	0,09	5,3	0,11	6,3
Muestra 7	96	4,16	0,18	4,3	0,26	6,2	0,26	6,2
Muestra 8	96	7,28	0,35	4,8	0,50	6,9	0,50	6,9

* CV (%): Coeficiente de variación (%)

Efecto Hook

No se detectó ningún efecto Hook en las concentraciones de IGFBP-7 de 4000 ng/mL.

No se detectó ningún efecto Hook en las concentraciones de TIMP-2 de 250 ng/mL.

Especificidad analítica

Se ha establecido la especificidad analítica del ensayo VIDAS® NEPHROCHECK® a través del análisis de compuestos de reacción cruzada de acuerdo con las recomendaciones incluidas en el documento EP07-Ed3 del CLSI. La reactividad cruzada se ha analizado mediante la sobrecarga de las muestras con compuestos de reacción cruzada.

Los resultados de este estudio se muestran en la siguiente tabla.

Componentes analizados	Concentración analizada (ng/mL)	Reactividad cruzada % TIMP-2 (%)	Reactividad cruzada % IGFBP-7 (%)
Proteína de unión al factor de crecimiento similar a la insulina 1 (IGFBP-1)	100	N/A*	7.3
Proteína de unión al factor de crecimiento similar a la insulina 2 (IGFBP-2)	250	N/A	2,3
Factor de crecimiento 1 similar a la insulina (IGF-1)	1500	N/A	0,5
Factor de crecimiento 2 similar a la insulina (IGF-2)	1500	N/A	0,7
Inhibidor de metaloproteinasa 1 (TIMP-1)	3000	< 0,1	N/A
Inhibidor de metaloproteinasa 3 (TIMP-3)	2500	< 0,1	N/A
Inhibidor de metaloproteinasa 4 (TIMP-4)	600	0,1	N/A

*N/A: No aplicable

Estudio de fármacos y otras sustancias con capacidad interferente

Se han estudiado las posibles interferencias de fármacos de uso común y otras sustancias de acuerdo con las recomendaciones incluidas en el documento EP07-Ed3 del CLSI. No se detectó ninguna interferencia significativa hasta las concentraciones que se indican a continuación:

Fármacos y sustancias endógenas	Concentración máxima (mg/L)
Paracetamol (Acetaminofeno)	201
Acetona	697
Ácido acetilsalicílico (Aspirina)	652
Albúmina	6900
Amoxicilina	75
Ácido ascórbico	52,5
Bicarbonatos	2940
Bilirrubina (conjugada)	400
Cafeína	108
Ciprofloxacino	12
Metamizol (dipirona/noramidopirina)	9600
Dopamina	1
Etanol	6000
Fentanilo	100
Furosemida	60
Glucosa D	9909
Anticuerpos humanos antirratón (HAMA)	2

Fármacos y sustancias endógenas	Concentración máxima (mg/L)
Hemoglobina	60
Heparina	21
Hidrocodona	0,2
Ibuprofeno	500
Insulina	0,003
Lisinoprilo	0,3
Azul de metileno	3,9
Metoprolol	5
Midazolam	3,76
Morfina	7,8
Mioglobina	5
Ondansetrón	0,342
Propofol	48
Riboflavina	12
Ácido salicílico	599
Vancomicina	120

Componentes habituales en la orina	Concentración máxima (mg/L)
Creatinina	1800
Urea	32000

No se observó ninguna interferencia de la albúmina hasta la concentración de 6900 mg/L. Por encima de esta concentración, la interferencia lleva a un aumento de la puntuación AKIRISK™.

No se observó ninguna interferencia de la hemoglobina hasta la concentración de 60 mg/L. Por encima de esta concentración, la interferencia lleva a un aumento de la puntuación AKIRISK™.

Tenga cuidado cuando interprete el resultado del ensayo VIDAS® NEPHROCHECK® en pacientes con proteinuria o hematuria marcadas.

Efectos del pH de la muestra de orina

Para el ensayo VIDAS® NEPHROCHECK®, se ha analizado el efecto del pH de la muestra de orina y no se han detectado interferencias significativas dentro del intervalo de pH [4-10].

Rendimiento clínico

Se ha analizado el rendimiento clínico del ensayo VIDAS® NEPHROCHECK® con una cohorte de 339 pacientes de interés.

Se involucró, de forma prospectiva, a sujetos adultos procedentes de 19 hospitales de puntos geográficos diversos de los Estados Unidos. No se incluyó a ningún paciente que presentase un cuadro de lesión renal aguda moderada o grave.

En el momento de la inclusión, se recogió una muestra de orina que se congeló y almacenó a ≤ −60 °C hasta su medición.

Tres laboratorios independientes participaron en las pruebas de las muestras. La muestra de cada uno de los sujetos se midió una sola vez en uno de los tres laboratorios independientes.

Un comité de validación clínica (CAC, por sus siglas en inglés) se encargó de la validación de cada uno de los sujetos que conformaron la cohorte de pacientes de interés. De los 339 pacientes de interés, 283 (83,5 %) se clasificaron como “Sin LRA” y 56 (16,5 %) como “Con LRA”.

Se validó el rendimiento de la prueba VIDAS® NEPHROCHECK® en un límite de 0,30. Los resultados obtenidos en el estudio muestran que los pacientes de interés con una puntuación AKIRISK™ ≤ 0,30 presentan un riesgo menor de desarrollar una LRA moderada o grave en un plazo de 12 horas tras el análisis, mientras que los pacientes de interés con una puntuación AKIRISK™ > 0,30 presentan un riesgo de desarrollar una LRA moderada o grave mayor en un plazo de 12 horas tras el análisis.

La siguiente tabla muestra la frecuencia de una puntuación AKIRISK™ > 0,30 en comparación con una puntuación ≤ 0,30 según el estado de LRA.

	Estado de LRA		Número total de resultados de la prueba VIDAS® NEPHROCHECK®
	Con LRA	Sin LRA	
Puntuación AKIRISK™ > 0,30	50 (14,8 %) Verdadero positivo	156 (46,0 %) Falso positivo	206
Puntuación AKIRISK™ ≤ 0,30	6 (1,8 %) Falso negativo	127 (37,5 %) Verdadero negativo	133
Número total de resultados de la prueba VIDAS® NEPHROCHECK®	56	283	339

Los datos de la tabla siguiente muestran una sensibilidad (que equivale a la tasa de verdaderos positivos o TPR, por sus siglas en inglés) del 89,3 % para un límite de puntuación AKIRISK™ de 0,30. Ello implica que la puntuación AKIRISK™ fue > 0,30 en el 89,3 % de los pacientes que mostraron una LRA moderada o grave en un plazo de 12 horas tras el análisis de riesgo de LRA en pacientes. La tasa de falsos negativos (que equivale a 1-sensibilidad o FNR, por sus siglas en inglés) es del 10,7 %, lo que indica que la puntuación AKIRISK™ fue ≤ 0,30 en el 10,7 % de los pacientes que mostraron una LRA moderada o grave en un plazo de 12 horas tras el análisis del riesgo de LRA en pacientes.

Los datos también muestran una especificidad (que equivale a la tasa de verdaderos negativos o TNR, por sus siglas en inglés) del 44,9 %. Ello implica que la puntuación AKIRISK™ fue ≤ 0,30 en el 44,9 % de los pacientes que no mostraron una LRA moderada o grave en un plazo de 12 horas tras el análisis de riesgo de LRA en pacientes. La tasa de falsos positivos (que equivale a 1-especificidad o FPR, por sus siglas en inglés) es del 55,1 %, lo que indica que la puntuación AKIRISK™ fue > 0,3 en el 55,1 % de los pacientes que no mostraron una LRA moderada o grave en un plazo de 12 horas tras el análisis del riesgo de LRA en pacientes.

Estadísticas Límite: 0,30	Valor %	[IC del $_{95\%}$]* %
Sensibilidad (TPR)	89,3	[78,5-95,0]
Especificidad (TNR)	44,9	[39,2-50,7]
FPR (1-especificidad)	55,1	[49,3-60,8]
FNR (1-sensibilidad)	10,7	[5,0-21,5]
Valor predictivo negativo (VPN)	95,5	[90,4-98,3]
Valor predictivo positivo (VPP)	24,3	[18,9-30,6]

* IC = Intervalo de confianza

También se ha validado el rendimiento clínico en los pacientes de interés con un segundo límite de 2,00.

La siguiente tabla muestra la frecuencia de una puntuación AKIRISK™ > 2,00 en comparación con una puntuación ≤ 2,00 según el estado de LRA.

	Estado de LRA		Número total de resultados de la prueba VIDAS® NEPHROCHECK®
	Con LRA	Sin LRA	
Puntuación AKIRISK™ > 2,00	29 (8,6 %) Verdadero positivo	22 (6,5 %) Falso positivo	51
Puntuación AKIRISK™ ≤ 2,00	27 (8,0 %) Falso negativo	261 (77,0 %) Verdadero negativo	288

	Estado de LRA		Número total de resultados de la prueba VIDAS® NEPHROCHECK®
	Con LRA	Sin LRA	
Número total de resultados de la prueba VIDAS® NEPHROCHECK®	56	283	339

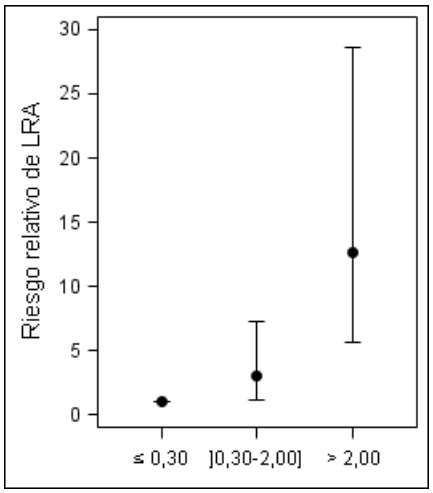
Los datos de la tabla siguiente muestran el rendimiento de la prueba VIDAS® NEPHROCHECK® para un límite de puntuación de 2,00.

Estadísticas Límite: 2,00	Valor %	[IC del 95%]* %
Sensibilidad (TPR)	51,8	[39,0-64,3]
Especificidad (TNR)	92,2	[88,5-94,8]
FPR (1-especificidad)	7,8	[5,2-11,5]
FNR (1-sensibilidad)	48,2	[35,7-61,0]
Valor predictivo negativo (VPN)	90,6	[86,7-93,5]
Valor predictivo positivo (VPP)	56,9	[43,3-69,5]

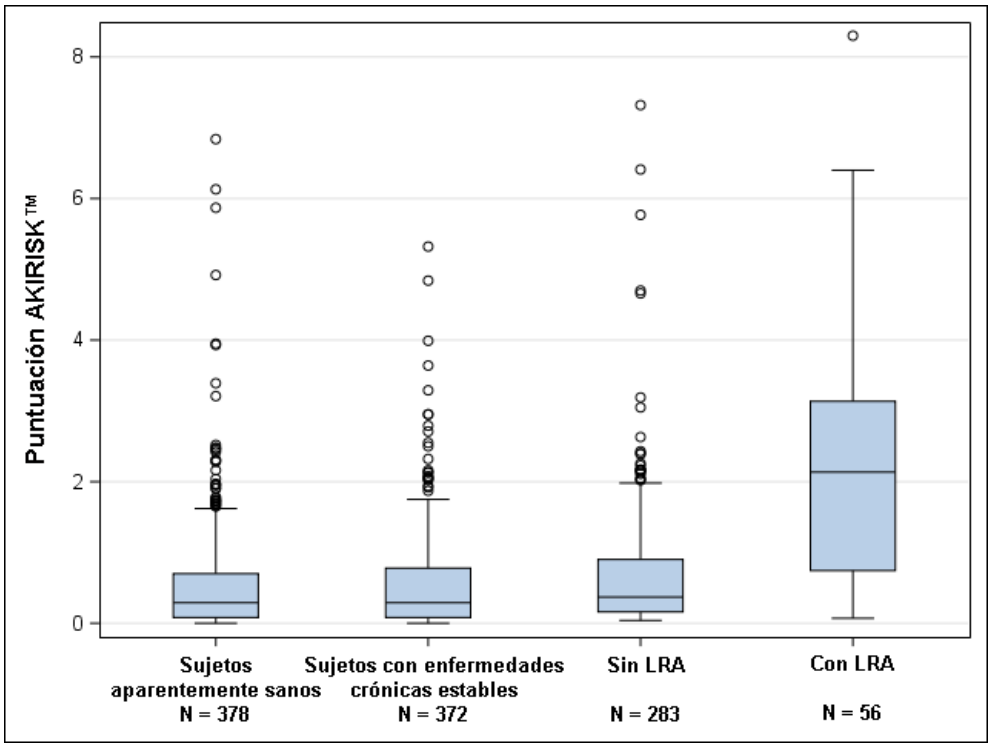
* IC = Intervalo de confianza

Tomando los resultados obtenidos en este estudio clínico como referencia, se ha calculado el riesgo absoluto de cada estrato: con un valor inferior o igual al límite de 0,30 (estrato 1), un valor comprendido entre los límites 0,30 y 2,0 (estrato 2) y un valor superior al límite de 2,0 (estrato 3). Se ha observado que el riesgo absoluto de LRA moderada o grave (estadio 2-3) aumenta a medida que aumenta el estrato de la siguiente forma: en el estrato 1, riesgo = 4,5 % (IC del 95 %, 1,0-8,0); en el estrato 2, riesgo = 13,5 % (IC del 95 %, 8,2-18,9); en el estrato 3, riesgo = 56,9 % (IC del 95 %, 43,3-70,5). Se calcularon los riesgos relativos correspondientes.

En comparación con los pacientes que han obtenido un valor en la prueba igual o inferior al límite de 0,30 (≤ 0,30), los pacientes con una puntuación AKIRISK™ comprendida entre los límites 0,30 y 2,00 presentan un riesgo 3 veces mayor (IC del 95 %, 1,2-7,2) de desarrollar LRA moderada o grave (estadio 2-3) en las siguientes 12 horas, mientras que los pacientes con una puntuación AKIRISK™ superior a 2,00 presentan un riesgo 12,6 veces mayor (IC del 95 %, 5,6-28,6) de desarrollarla (ver gráfico siguiente).



Las distribuciones de las puntuaciones AKIRISK™ de los pacientes de interés “Con LRA” y “Sin LRA” se muestran en la siguiente figura. También se muestran, a modo comparativo, las distribuciones de los resultados de la prueba VIDAS® NEPHROCHECK® de los sujetos de la cohorte de sujetos aparentemente sanos y la cohorte de sujetos con enfermedades crónicas estables (descritos en la sección Intervalo de referencia).



Las distribuciones de las puntuaciones AKIRISK™ de los sujetos aparentemente sanos, los sujetos con enfermedades crónicas estables (sin enfermedad aguda) y los pacientes de interés “Sin LRA” son similares. En cambio, las puntuaciones AKIRISK™ son considerablemente altas en el caso de los pacientes de interés con LRA si se comparan con los resultados de individuos sanos en apariencia, individuos con enfermedades crónicas o pacientes sin LRA en los que esté indicado el uso.

La siguiente tabla muestra la información demográfica y otra información de referencia relativa a los pacientes de interés de este estudio clínico con respecto todos los sujetos, a los sujetos con LRA y a los sujetos sin LRA.

Características demográficas		Todos N total = 339	Sin LRA N total = 283	Con LRA N total = 56
		N (%), media (DE), mediana (IQR)	N (%), media (DE), mediana (IQR)	N (%), media (DE), mediana (IQR)
Edad (años)	Media (DE)*	62 (17)	63 (17)	61 (17)
	Mediana (IQR)**	65 (52-76)	66 (52-76)	62 (51-76)
IMC (kg/m^2)	Media (DE)*	30,8 (9,1)	29,9 (8,3)	35,3 (11,3)
	Mediana (IQR)**	28,6 (25,0-34,5)	27,8 (24,3-33,6)	31,8 (26,6-40,4)
Sexo	Mujer	168 (49,6)	139 (49,1)	29 (51,8)
	Hombre	171 (50,4)	144 (50,9)	27 (48,2)

Características demográficas		Todos N total = 339	Sin LRA N total = 283	Con LRA N total = 56
		N (%), media (DE), mediana (IQR)	N (%), media (DE), mediana (IQR)	N (%), media (DE), mediana (IQR)
Causa del ingreso hospitalario***	Cardiovascular	108 (31,9)	88 (31,1)	20 (35,7)
	Cerebrovascular	41 (12,1)	38 (13,4)	3 (5,4)
	Sepsis	70 (20,6)	55 (19,4)	15 (26,8)
	Respiratoria/Pulmonar	151 (44,5)	127 (44,9)	24 (42,9)
	Traumatismo	41 (12,1)	36 (12,7)	5 (8,9)
	Intervención quirúrgica (cualquier tipo)	87 (25,7)	79 (27,9)	8 (14,3)
	Intervención quirúrgica (emergencia)	47 (13,9)	44 (15,5)	3 (5,4)
	Intervención quirúrgica (programada)	40 (11,8)	35 (12,4)	5 (8,9)
	Gastrointestinal	41 (12,1)	35 (12,4)	6 (10,7)
	Otras	114 (33,6)	93 (32,9)	21 (37,5)
Causa del ingreso en la UCI***	Cardiovascular	126 (37,2)	104 (36,7)	22 (39,3)
	Cerebrovascular	46 (13,6)	42 (14,8)	4 (7,1)
	Sepsis	83 (24,5)	65 (23,0)	18 (32,1)
	Respiratoria	181 (53,4)	152 (53,7)	29 (51,8)
	Traumatismo	39 (11,5)	34 (12,0)	5 (8,9)
	Intervención quirúrgica/ posoperatorio	91 (26,8)	83 (29,3)	8 (14,3)
	Otras	110 (32,4)	86 (30,4)	24 (42,9)
Tipo de UCI	Cirugía cardíaca	33 (9,7)	29 (10,2)	4 (7,1)
	UCI mixta	37 (10,9)	31 (11,0)	6 (10,7)
	Unidad coronaria	9 (2,7)	7 (2,5)	2 (3,6)
	Médica	170 (50,1)	143 (50,5)	27 (48,2)
	Neurológica	9 (2,7)	7 (2,5)	2 (3,6)
	Otras	7 (2,1)	6 (2,1)	1 (1,8)
	Quirúrgica	48 (14,2)	41 (14,5)	7 (12,5)
	Traumatismo	26 (7,7)	19 (6,7)	7 (12,5)

*DE: Desviación estándar

**IQR: Rango intercuartílico (50 % central)

***Los sujetos pueden tener varias causas para el ingreso hospitalario.

Eliminación de los residuos

Eliminar tanto los reactivos usados como los no utilizados, así como los materiales desechables contaminados siguiendo los procedimientos relativos con los productos infecciosos o potencialmente infecciosos.

Es responsabilidad de cada laboratorio la gestión de los desechos y efluentes que produce según su naturaleza y peligrosidad, garantizando (o haciendo garantizar) su tratamiento y eliminación, según las reglamentaciones aplicables.

Referencias bibliográficas

1. Degeorges, A., Wang, F., Frierson, H. F., Jr., Seth, A., and Sikes, R. A. (2000) - Distribution of IGFBP-rP1 in normal human tissues. - *J. Histochem. Cytochem.* 48, 747-754.

2. Yang, Q. H., Liu, D. W., Long, Y., Liu, H. Z., Chai, W. Z., and Wang, X. T. (2009) - Acute renal failure during sepsis: potential role of cell cycle regulation. -*J. Infect.* 58, 459-464.
3. Burger, A. M., Leyland-Jones, B., Banerjee, K., Spyropoulos, D. D., and Seth, A. K. (2005) - Essential roles of IGFBP-3 and IGFBP-rP1 in breast cancer. - *Eur. J. Cancer* 41, 1515-1527.
4. Ahmed, S., Yamamoto, K., Sato, Y., Ogawa, T., Herrmann, A., Higashi, S., and Miyazaki, K. (2003) - Proteolytic processing of IGFBP-related protein-1 (TAF/angiomodulin/mac25) modulates its biological activity. - *Biochem. Biophys. Res. Commun.* 310, 612-618.
5. Sato, Y., Chen, Z., and Miyazaki, K. (2007) - Strong suppression of tumor growth by insulin-like growth factor-binding protein-related protein 1/tumor-derived cell adhesion factor/mac25. - *Cancer Sci.* 98, 1055-1063.
6. Usui, T., Murai, T., Tanaka, T., Yamaguchi, K., Nagakubo, D., Lee, C. M., Kiyomi, M., Tamura, S., Matsuzawa, Y., and Miyasaka, M. (2002) - Characterization of mac25/angiomodulin expression by high endothelial venule cells in lymphoid tissues and its identification as an inducible marker for activated endothelial cells. - *Int. Immunol.* 14, 1273-1282.
7. Sprenger, C. C., Vail, M. E., Evans, K., Simurdak, J., and Plymate, S. R. (2002) - Over-expression of insulin-like growth factor binding protein-related protein-1(IGFBP-rP1/mac25) in the M12 prostate cancer cell line alters tumor growth by a delay in G1 and cyclin A associated apoptosis. - *Oncogene* 21, 140-147.
8. Nousbeck, J., Sarig, O., Avidan, N., Indelman, M., Bergman, R., Ramon, M., Enk, C. D., and Sprecher, E. (2010) - Insulin-like growth factor-binding protein 7 regulates keratinocyte proliferation, differentiation and apoptosis. - *J. Invest Dermatol.* 130, 378-387.
9. Unigene, National Center for Biotechnology Information; https://www.ncbi.nlm.nih.gov/gene/7077. .
10. Protein Knowledgebase, UniProtKB/Swiss-Prot; http://www.uniprot.org/uniprot/P16035.
11. Covington, M. D., Burghardt, R. C., and Parrish, A. R. (2006) - Ischemia-induced cleavage of cadherins in NRK cells requires MT1-MMP (MMP-14). *Am. J. Physiol Renal Physiol* 290, F43-F51.
12. Caron, A., Desrosiers, R. R., and Beliveau, R. (2005) - Ischemia injury alters endothelial cell properties of kidney cortex: stimulation of MMP-9. - *Exp. Cell Res.* 310, 105-116.
13. Mannello, F., Luchetti, F., Falcieri, E., and Papa, S. (2005) - Multiple roles of matrix metalloproteinases during apoptosis. - *Apoptosis* 10, 19-24.
14. Le, N. T., Xue, M., Castelnoble, L. A., and Jackson, C. J. (2007) -The dual personalities of matrix metalloproteinases in inflammation. - *Front Biosci.* 12, 1475-1487.
15. Catania, J. M., Chen, G., and Parrish, A. R. (2007) - Role of matrix metalloproteinases in renal pathophysiologies. - *Am. J. Physiol Renal Physiol.* 292, F905-F911.
16. Stetler-Stevenson, W. G. (2008) - Tissue inhibitors of metalloproteinases in cell signaling: metalloproteinase-independent biological activities. - *Sci. Signal. 1* re6.
17. Devarajan, P. (2006) - Update on mechanisms of ischemic acute kidney injury. - *J Am Soc Nephrol.* 17, 1503–20.
18. Rodier, F., Campisi, J., Bhaumik, D. (2007) - Two faces of p53: aging and tumor suppression. - *Nucleic Acids Res.* 35, 7475–84.
19. Boonstra, J., Post, J.A. (2004) - Molecular events associated with reactive oxygen species and cell cycle progression in mammalian cells. *Gene* 337, 1–13.
20. Seo, D.W., Li, H., Qu, C.K., Oh, J., Kim, Y.S., Diaz, T., Wei, B., Han, J.W., Stetler-Stevenson, W.G. (2006) - Shp-1 mediates the antiproliferative activity of tissue inhibitor of metalloproteinase-2 in human microvascular endothelial cells. - *J Biol Chem.* 281, 3711–21.
21. Witzgall, R., Brown, D., Schwarz, C., Bonventre, J.V. (1994) - Localization of proliferating cell nuclear antigen, vimentin, c-Fos, and clusterin in the postischemic kidney. Evidence for a heterogenous genetic response among nephron segments, and a large pool of mitotically active and dedifferentiated cells. - *J Clin Invest.* 93, 2175–88.
22. Price, P.M., Safirstein, R.L., Megyesi, J. (2009) - The cell cycle and acute kidney injury. - *Kidney Int.* 76, 604–13.
23. Kashani, K., Al-Khafaji, A., Ardiles, T., Artigas, A., Bagshaw, S.M., *et al.* (2012) - Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. - *Crit Care.* 17, R25. http://ccforum.com/content/17/1/R25.
24. Uchino, S., Kellum, J. A., Bellomo, R., Doig, G. S., Morimatsu, H., Morgera, S., Schetz, M., Tan, I., Bouman, C., Macedo, E., Gibney, N., Tolwani, A., and Ronco, C. - Acute renal failure in critically ill patients: a multinational, multicenter study. - *JAMA* 294, 813-818 (2005).
25. Mehta, R. L., Pascual, M. T., Soroko, S., Savage, B. R., Himmelfarb, J., Ikizler, T. A., Paganini, E. P., and Chertow, G. M. - Spectrum of acute renal failure in the intensive care unit: the PICARD experience. - *Kidney Int.* 66, 1613-1621 (2004).
26. Waikar, S. S., Liu, K. D., and Chertow, G. M. - Diagnosis, epidemiology and outcomes of acute kidney injury. - *Clin. J. Am. Soc. Nephrol.* 3, 844-861 (2008).
27. Kellum, J. A. - Acute kidney injury. - *Crit Care Med.* 36, S141-S145 (2008).
28. Xue, J. L., Daniels, F., Star, R. A., Kimmel, P. L., Eggers, P. W., Molitoris, B. A., Himmelfarb, J., and Collins. - A. J. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. - *J. Am. Soc. Nephrol.* 17, 1135-1142 (2006).

29. McCullough, P. A., Adam, A., Becker, C. R., Davidson, C., Lameire, N., Stacul, F., and Tumlin - J. Epidemiology and prognostic implications of contrast-induced nephropathy. - *Am. J. Cardiol.* 98, 5K-13K (2006).
30. Joannidis, M., Metnitz, B., Bauer, P., Schusterschitz, N., Moreno, R., Druml, W., and Metnitz, P. G. - Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. - *Intensive Care Med.* 35, 1692-1702 (2009).
31. Dasta, J. F., Kane-Gill, S. L., Durtschi, A. J., Pathak, D. S., and Kellum, J.A. - Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. - *Nephrol. Dial. Transplant.* 23, 1970-1974 (2008).
32. Bagshaw, S. M., George, C., Dinu, I., and Bellomo, R. - A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. - *Nephrol. Dial. Transplant.* 23, 1203-1210 (2008).
33. Hoste, E. A., Clermont, G., Kersten, A., Venkataraman, R., Angus, D. C., De, B. D., and Kellum, J. A. - RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. - *Crit Care* 10, R73 (2006).
34. Chertow, G. M., Burdick, E., Honour, M., Bonventre, J. V., and Bates, D. W. - Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. - *J. Am. Soc. Nephrol.* 16, 3365-3370 (2005).
35. Amdur, R. L., Chawla, L. S., Amodeo, S., Kimmel, P. L., and Palant, C. E. - Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. - *Kidney Int.* 76, 1089-1097 (2009).
36. Ishani, A., Xue, J. L., Himmelfarb, J., Eggers, P. W., Kimmel, P. L., Molitoris, B. A., and Collins, A. J. - Acute kidney injury increases risk of ESRD among elderly. - *J. Am. Soc. Nephrol.* 20, 223-228 (2009).
37. Mehta, R. L., Kellum, J. A., Shah, S. V., Molitoris, B. A., Ronco, C., Warnock, D. G., and Levin, A. - Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. - *Crit Care* 11, R31 (2007).
38. International Society of Nephrology (2012) - KDIGO Clinical Practice Guideline for Acute Kidney Injury. - *Kidney Int. Suppl.* 2, 1-138. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO%20AKI%20Guideline.pdf
39. WORLD HEALTH ORGANIZATION, USE OF ANTICOAGULANTS IN DIAGNOSTIC, LABORATORY INVESTIGATIONS, 2002, WHO/DIL/LAB/99.1 Rev.2
40. Hoste E.A.J., McCullough P.A., Kashani K., Chawla L.S., Joannidis M., Shaw A.D., Feldkamp T., Uettwiller-Geiger D.L., McCarthy P., Shi J., Walker M.G., and Kellum J.A. on behalf of the Sapphire Investigators. Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. *Nephrol Dial Transplant.* 2014;29:2054-61.
41. EP28-A3C: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline Third Edition (Definición, establecimiento y verificación de los intervalos de referencia en el laboratorio clínico; normas orientadoras aprobadas, tercera edición) (ISBN 1-56238-682-4) 2010.
42. EP05-A3: Evaluation of Precision of Quantitative Measurement Procedures; Approved Guideline – Third Edition (Evaluación de la precisión de los procedimientos de medición cuantitativa; normas orientadoras aprobadas, tercera edición) (ISBN 1-56238-968-8).

Tabla de símbolos

Símbolo	Significado
REF	Número de catálogo
IVD	Producto sanitario para diagnóstico *in vitro*
	Fabricante
	Límite de temperatura
	Fecha de caducidad
LOT	Código de lote
	Consulte las instrucciones de uso
	Contenido suficiente para <n> ensayos
	Fecha de fabricación

Garantía limitada

bioMérieux garantiza el rendimiento del producto para el uso previsto declarado siempre que todos los procedimientos para el uso, el almacenamiento y la manipulación, la vida útil (en su caso) y las precauciones se sigan estrictamente como se detalla en las instrucciones de uso.

A excepción de lo expresamente establecido anteriormente, bioMérieux por la presente renuncia a todas las garantías, incluyendo cualquier garantía implícita de comerciabilidad y adecuación para un propósito o uso particular, y se exime de toda responsabilidad, ya sea directa, indirecta o consecuente, de cualquier uso del reactivo, software, instrumento y desechables (el “Sistema”) distinto a lo que se indica en las instrucciones de uso.

Histórico de revisiones

Categoría de tipo de cambio

N/A	No aplica (primera modificación)
Corrección	Corrección de anomalías en la documentación
Cambio técnico	Adición, revisión y/o eliminación de información relativa al producto
Administrativo	Implementación de cambios no técnicos notables para el usuario

Nota: *Los cambios menores de errores tipográficos, gramaticales y de formato no aparecen incluidos en el historial de revisiones.*

Fecha de publicación	Versión	Tipo de cambio	Resumen de cambios
2020-12	054303-01	N/A	No aplica (primera modificación)
2022-03	054303-02	Administrativo	Contenido del kit / Instrucciones de uso
		Cambio técnico	Condiciones de almacenamiento

Para los usuarios de la Unión Europea (Reglamento (UE) 2017/746) y de los países con requisitos similares: Si ocurriera un incidente grave durante el uso de este dispositivo o como resultado de su uso, informe al fabricante o a su representante autorizado, así como a su autoridad nacional.

bioMérieux SA
376 Chemin de l'Orme
69280 Marcy-l’Etoile - France

673 620 399 RCS LYON
Tel. 33 (0)4 78 87 20 00
Fax 33 (0)4 78 87 20 90
www.biomerieux.com

CE 0459

JAMA Network Open

Consensus Statement | Critical Care Medicine

Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference
A Consensus Statement

Marlies Ostermann, MD, PhD; Alexander Zarbock, MD; Stuart Goldstein, MD; Kianoush Kashani, MD, MSc; Etienne Macedo, MD, PhD; Raghavan Murugan, MD; Max Bell, MD, PhD; Lui Forni, PhD, MBBS; Louis Guzzi, MD; Michael Joannidis, MD, PhD; Sandra L. Kane-Gill, PharmD, MSc; Matthieu Legrand, MD, PhD; Ravindra Mehta, MD; Patrick T. Murray, MD; Peter Pickkers, MD, PhD; Mario Plebani, MD; John Prowle, MD; Zaccaria Ricci, MD; Thomas Rimmelé, MD, PhD; Mitchell Rosner, MD; Andrew D. Shaw, MB; John A. Kellum, MD; Claudio Ronco, MD

Abstract

IMPORTANCE In the last decade, new biomarkers for acute kidney injury (AKI) have been identified and studied in clinical trials. Guidance is needed regarding how best to incorporate them into clinical practice.

OBJECTIVE To develop recommendations on AKI biomarkers based on existing data and expert consensus for practicing clinicians and researchers.

EVIDENCE REVIEW At the 23rd Acute Disease Quality Initiative meeting, a meeting of 23 international experts in critical care, nephrology, and related specialties, the panel focused on 4 broad areas, as follows: (1) AKI risk assessment; (2) AKI prediction and prevention; (3) AKI diagnosis, etiology, and management; and (4) AKI progression and kidney recovery. A literature search revealed more than 65 000 articles published between 1965 and May 2019. In a modified Delphi process, recommendations and consensus statements were developed based on existing data, with 90% agreement among panel members required for final adoption. Recommendations were graded using the Grading of Recommendations, Assessment, Development and Evaluations system.

FINDINGS The panel developed 11 consensus statements for biomarker use and 14 research recommendations. The key suggestions were that a combination of damage and functional biomarkers, along with clinical information, be used to identify high-risk patient groups, improve the diagnostic accuracy of AKI, improve processes of care, and assist the management of AKI.

CONCLUSIONS AND RELEVANCE Current evidence from clinical studies supports the use of new biomarkers in prevention and management of AKI. Substantial gaps in knowledge remain, and more research is necessary.

JAMA Network Open. 2020;3(10):e2019209.
Corrected on November 10, 2020. doi:10.1001/jamanetworkopen.2020.19209

Key Points

Question How can new biomarkers for acute kidney injury be integrated into routine clinical practice?

Findings In this consensus statement, a 23-expert panel developed 11 recommendations for the use of new stress, functional, and damage biomarkers in clinical practice to prevent and manage acute kidney injury. In addition, gaps in knowledge and areas for more research were identified.

Meaning The integration of appropriately selected biomarkers in routine clinical practice has potential to improve acute kidney injury care.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Acute kidney injury (AKI) is common in hospitalized adults and children and associated with serious complications and high health care costs. Traditionally, 2 functional biomarkers, serum creatinine (sCr) and urine output, are used to define AKI,[1] but these markers are limited by delayed changes following kidney injury and have low sensitivity and specificity. Several novel biomarkers have been shown to detect AKI earlier and are more sensitive than sCr (**Table**).[2-19] For any prevention strategies

Table. Description and Characteristics of Common Biomarkers of AKI

AKI biomarker	Biological role	Source	Stress marker[a]	Damage marker[b]	Functional marker[c]	Potential role in clinical practice				
						Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI	Kidney recovery
Alanine aminopeptidase; alkaline phosphatase; γ-glutamyl transpeptidase	Enzymes located on the brush border villi of the proximal tubular cells; released into urine after tubular damage	Coca et al,[2] 2008		Urine				X	X	
Calprotectin	Cytosolic calcium-binding complex; derived from neutrophils and monocytes; detectable in urine in intrinsic AKI	Charlton et al,[3] 2014; Heller et al,[4] 2011		Urine				X		
C-C motif chemokine ligand 14	Pro-inflammatory chemokine; released into urine following stress or damage of tubular cells	Hoste et al,[5] 2020		Urine						X
Chitinase 3-like protein 1	39 kDa intracellular protein of glycoside hydrolase family; expressed by endothelial cells, macrophages, and neutrophils	De Loor et al,[6] 2016		Urine and plasma				X		
Cystatin C	13 kDa cysteine protease inhibitor produced by nucleated human cells; freely filtered	Coca et al,[2] 2008; Ho et al,[7] 2015; Ravn et al,[8] 2019			Plasma			X	X	
Dickkopf-3	38 kDa stress-induced, kidney tubular epithelia-derived glycoprotein; secreted into urine under tubular stress conditions	Schunk et al,[9] 2019	Urine			X	X			
α glutathione S-transferase	Cytoplasmic enzyme in proximal tubule	Koyner at al,[10] 2010		Urine				X		
π glutathione S-transferase	Cytoplasmic enzyme in distal tubules	Coca et al,[2] 2008; Charlton et al,[3] 2014		Urine				X		
Hepatocyte growth factor	Antifibrotic cytokine produced by mesenchymal cells and involved in tubular cell regeneration after AKI	Heller et al,[4] 2011; Vaidya et al,[11] 2008		Plasma					X	X
Hepcidin	2.78 kDa peptide hormone predominantly produced in hepatocytes; freely filtered	Ho et al,[7] 2015		Urine and plasma				X	X	
Tissue metalloproteinase-2; insulin-like growth factor binding protein-7	Metalloproteinases released during cell cycle arrest	Kashani et al,[12] 2013; Ostermann et al,[13] 2018; Joannidis et al,[14] 2019	Urine				X	X	X	
Interleukin-18	18 kDa pro-inflammatory cytokine; released into urine following tubular damage	Coca et al,[2] 2008; Ho et al,[7] 2015		Urine			X	X		
Kidney injury molecule-1	Transmembrane glycoprotein produced by proximal tubular cell; released into urine after tubular damage	Coca et al,[2] 2008; Ho et al,[7] 2015; Koyner et al,[10] 2010		Urine			X	X	X	
Liver-type fatty acid-binding protein	14 kDa intracellular lipid chaperone; freely filtered and reabsorbed in proximal tubule; urinary excretion after tubular cell damage	Ho et al,[7] 2015		Urine and plasma				X		
MicroRNA	Endogenous single-stranded non-coding nucleotides; >50 individual microRNAs are expressed in AKI, especially in association with inflammation, apoptosis and fibrosis	Fan et al,[15] 2019		Urine and plasma				X		
Monocyte chemoattractant peptide-1	Peptide expressed in tubular epithelial cells, kidney mesangial cells and podocytes; released into urine	Moledina et al,[16] 2017		Urine					X	
N-acetyl-β-D-glucosaminidase	>130 kDa lysosomal enzyme; released into urine after tubular damage	Charlton et al,[3] 2014		Urine				X		
Neutrophil gelatinase-associated lipocalin	At least 3 different types: (1) monomeric 25 kDa glycoprotein produced by neutrophils and epithelial tissues, including tubular cells; (2) homodimeric 45 kDa protein produced by neutrophils; (3) heterodimeric 135 kDa protein produced by tubular cells	Coca et al,[2] 2008; Ho et al,[7] 2015; Charlton et al,[3] 2014		Urine and plasma				X	X	

(continued)

Table. Description and Characteristics of Common Biomarkers of AKI (continued)

AKI biomarker	Biological role	Source	Stress marker[a]	Damage marker[b]	Functional marker[c]	Potential role in clinical practice				
						Risk assessment	Prediction of AKI	Diagnosis of AKI	Severity of AKI	Kidney recovery
Netrin-1	50-75 kDa laminin-related molecule minimally expressed in proximal tubular cells of normal kidneys; released into urine after tubular cell damage	Ramesh et al,[17] 2010		Urine				X		
Osteopontin	Glycoprotein expressed in tubular cells and interstitial infiltrating cells in areas of tubulointerstitial damage	Lorenzen et al,[18] 2011		Plasma				X	X	
Proenkephalin A	Endogenous polypeptide hormone in adrenal medulla, nervous system, immune system and renal tissue; freely filtered	Legrand et al,[19] 2019			Plasma			X	X	X
Retinol binding protein	21 kDa glycoprotein; synthesized by liver; filtered by glomeruli and reabsorbed by proximal tubules; released into urine following tubular damage	Charlton et al,[3] 2014		Plasma						
Tumor necrosis factor	Pro-inflammatory cytokine; released after tubular damage	Ho et al,[7] 2015		Plasma				X		

Abbreviation: AKI, acute kidney injury.

[a] Stress markers indicate cell stress; cell stress can resolve or progress to damage or alter kidney function.

[b] Damage markers indicate structural damage that may or may not be associated with reduced kidney function. These molecules include constitutive proteins released by the damaged kidney, molecules upregulated in response to injury, or nonkidney tissue products that are filtered, reabsorbed, or secreted by the kidney.

[c] Functional markers reflect changes in glomerular filtration.

to be effective, patients with high risk need to be identified before kidney insults result in kidney damage, and AKI needs to be diagnosed as early as possible.

In 2011, the 10th Acute Disease Quality Initiative (ADQI) meeting focused on AKI biomarkers and their application in clinical practice.[20] The expert committee concluded that the evidence for AKI biomarkers was limited and insufficient for recommendations and that more research and strategies toward the adoption of biomarkers in clinical practice were needed. Subsequently, new AKI biomarkers have been discovered, clinical trials have been completed, and some biomarkers have gained official regulatory approval.[12,21-23] In 2019, an ADQI meeting was called to review this new evidence and to develop recommendations regarding AKI risk assessment, prediction, prevention, diagnosis, management, and kidney recovery for practicing clinicians and researchers.

Methods

The 23rd ADQI consensus meeting followed established ADQI methods to provide statements based on existing evidence and professional judgement and to identify clinical research priorities.[24] The consensus process incorporated a multistep modified Delphi method. In early 2019, the steering group identified 4 broad topics (eTable 1 in the Supplement) and invited a 23-expert panel, representing nephrology, critical care medicine, surgery, anesthesia, pediatrics, clinical biochemistry, and pharmacy. The project followed the ADQI methods as outlined in the this section. The article summarizes the conclusions of an international expert panel. The conclusions are based on the existing evidence in the literature. Therefore, institutional approval was not required. All panelists consented to their inclusion in this article. This report followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) reporting guideline.

The working groups determined the key questions and identified relevant literature by searching PubMed, MEDLINE, Embase, the Cochrane Library, ClinicalTrials.gov, and Cochrane Controlled Trials Register, using the terms *acute kidney injury* or *AKI* and *biomarker*, combined with *risk*, *diagnosis*, *etiology*, *prevention*, *management*, *prediction*, or *prognosis*. Because of the volume of retrieved literature (>65 000 articles), representative publications were selected[2,5,7,9,10,19,25-46] (eTable 2 in the Supplement). Articles were eligible if they were prospective or retrospective cohort studies, case-control studies, randomized clinical trials, or systematic reviews evaluating the role of serum or urinary biomarkers for AKI. Each working group drafted recommendations and consensus statements. Recommendations were graded based on the Grading of Recommendations Assessment, Development, and Evaluation system (eTable 3 in the Supplement). At a face-to-face meeting of all 23 panelists in Padova, Italy, from May 30 to June 2, 2019, each group presented their statements and recommendations. Panel members discussed the statements until agreement was reached regarding whether to retain, modify, or eliminate them. Only panelists who attended the face-to-face meeting participated in the discussion and final approval. Statements required 90% agreement from the panel to be included in the final document. The contributions of all groups were merged and reconciled by the steering group. The final document was approved by all panelists. Here, we report the conclusions.

Results

Biomarkers for AKI Risk Assessment

AKI is often already established when patients present with acute illness. Clearly, the implementation of primary prevention is not possible in these cases. However, situations in which elective clinical interventions or exposures place patients at risk of AKI provide opportunities to modify factors that contribute to AKI development and progression.

Consensus Statement 1

The decision to perform a Kidney Health Assessment (KHA) to gauge AKI susceptibility should integrate patient factors, including demographic characteristics, comorbidities, and previous AKI episodes with the expected intensity of a planned exposure that carries AKI risk. This recommendation received a grade of B, strong.

Predisposing factors, susceptibility, and intensity of precipitating factors determine the risk of AKI. The ADQI 22 working group developed a flow diagram outlining KHA of AKI susceptibility, which incorporates previous AKI history, blood pressure, chronic kidney disease (CKD) and drugs and/or dipstick[47] (eFigure 1 in the Supplement). Two elective exposures that carry a particularly high AKI risk are major surgery and nephrotoxic medications.

Consensus Statement 2

The types of functional and/or damage biomarker evaluation to be performed should be driven by the results of the KHA for AKI susceptibility. This recommendation received a grade of B, strong.

The KHA for AKI susceptibility (eFigure 1 in the Supplement) includes the assessment of CKD/creatinine and dipstick (ie, proteinuria/albuminuria) both before and after a planned exposure associated with AKI risk.[47] Traditional measures of kidney function include sCr, creatinine-based estimated glomerular filtration rate (eGFR) equations, serum cystatin C, cystatin plus creatinine–based eGFR equations, and selective techniques to measure GFR in high-risk patients.[48] Kidney damage can be assessed by estimating or measuring urinary protein excretion.[29,43]

New biomarkers and techniques are emerging that may allow better prediction of AKI risk.[9,32] A study of 733 patients who underwent cardiac surgery demonstrated that the preoperative urinary concentration of dickkopf-3, a urinary cytokine and tubular stress biomarker, predicted the development of postoperative AKI and kidney function loss with an area under the receiver operating characteristic curve (AUROC) of 0.78.[9]

Consensus Statement 3

We suggest that biomarkers of acute damage are not interpretable prior to a kidney insult and should not be used for AKI risk assessment. This recommendation received a grade of A, strong.

It is unlikely that patients scheduled to undergo nephrotoxic exposures or elective surgery in stable conditions will meet the criteria for kidney stress or acute damage to be predictive of subsequent AKI. However, future AKI biomarkers in patients with specific clinical risk stratification may help to detect those at risk of kidney complications after exposure. It is also plausible that markers of kidney fitness may be discovered, including in patients with normal GFR.

Biomarkers for AKI Prediction and Prevention

AKI affects approximately 15% of hospital admissions.[49] Management is mainly focused on prevention and supportive care.[21] In certain clinical settings, 20% to 30% of AKI cases are considered preventable.[50]

Consensus Statement 4

We recommend using validated biomarkers to identify patient populations for whom preventive interventions have been shown to improve outcomes. This recommendation received a grade of A, strong.

The performance of current prediction models to identify patients at risk of AKI is variable.[51-55] The negative predictive value is generally good, but the positive predictive value of most models is moderate to low. In susceptible patients exposed to injurious events, validated biomarkers can predict the development or progression of AKI and may provide opportunities for intervention.[21,22,28,35] Trials have demonstrated that timely initiation of preventive strategies in patients with positive stress biomarkers after a kidney insult, ie, tissue inhibitor of metalloproteinases 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7) were

effective at preventing AKI.[21,22] The patients in the Prevention of AKI trial were randomized based on patients who had an urinary concentration of TIMP-2 × IGFBP7 of at least 0.3 $(ng/mL)^2/1000$ after cardiac surgery to protocolized vs standard care. At 72 hours, there was a 17% reduction in AKI. A similar approach was followed in the Biomarker-Guided Intervention to Prevent Acute Kidney Injury After Major Surgery study.[22] Patients undergoing major abdominal surgery were randomized to intervention vs standard care.[22] There was a 13% reduction in AKI stages 2 and 3. Similarly, the implementation of a nephrology rapid response team that used TIMP-2 × IGFBP7 monitoring to identify at-risk patients for preventative Kidney Disease Improving Global Outcomes (KDIGO) strategies reduced the need for kidney replacement therapy (KRT).[56]

The use of functional biomarkers may also optimize drug dosing. For decades, sCr has been used for this purpose. However, the use of sCr or any sCr-based estimate requires kidney function to be at a steady state. Cystatin C is less reliant on muscle mass and dietary intake and offers an alternative approach to estimate GFR. Reports indicate that in a steady state, eGFR estimated by creatinine–cystatin C is more precise and accurate at determining a measured GFR than eGFR estimated by creatinine or cystatin C alone.[8,57] The use of CKD Epidemiology Collaboration (CKD-EPI) eGFR including creatinine and cystatin C in a vancomycin dosing algorithm improved the achievement of target vancomycin trough concentrations by 22% compared with historical controls using CKD-EPI eGFR estimated with creatinine alone.[58-60] For life-saving drugs with potential nephrotoxic effects, the concomitant use of functional and damage biomarkers has the potential to provide important information to gauge dosing and duration of treatment and to prevent AKI.[13,61]

Consensus Statement 5

We suggest combining clinical assessment and validated biomarkers to triage patients and optimize the timing and type of interventions designed to improve processes of care and patient outcomes. This recommendation received a grade of C, strong.

Combining the clinical assessment and traditional tests with new AKI biomarkers provides information that may change processes of care and guide therapy. Negative results can be valuable, too.[14,62] For instance, critically ill patients with oliguria and urinary TIMP-2 × IGFBP7 of less than 0.3 $(ng/mL)^2/1000$ do not have an increased risk of progressing to more severe AKI.[14] Repeated biomarker testing may be relevant, too, depending on the change in patient risk profile.

Biomarkers for AKI Diagnosis, Etiology, and Management

There is a persistent unmet need for an earlier identification of patients with AKI. Furthermore, diagnostic tools that identify the location, mechanism, etiology, severity, and prognosis of AKI are necessary.[63]

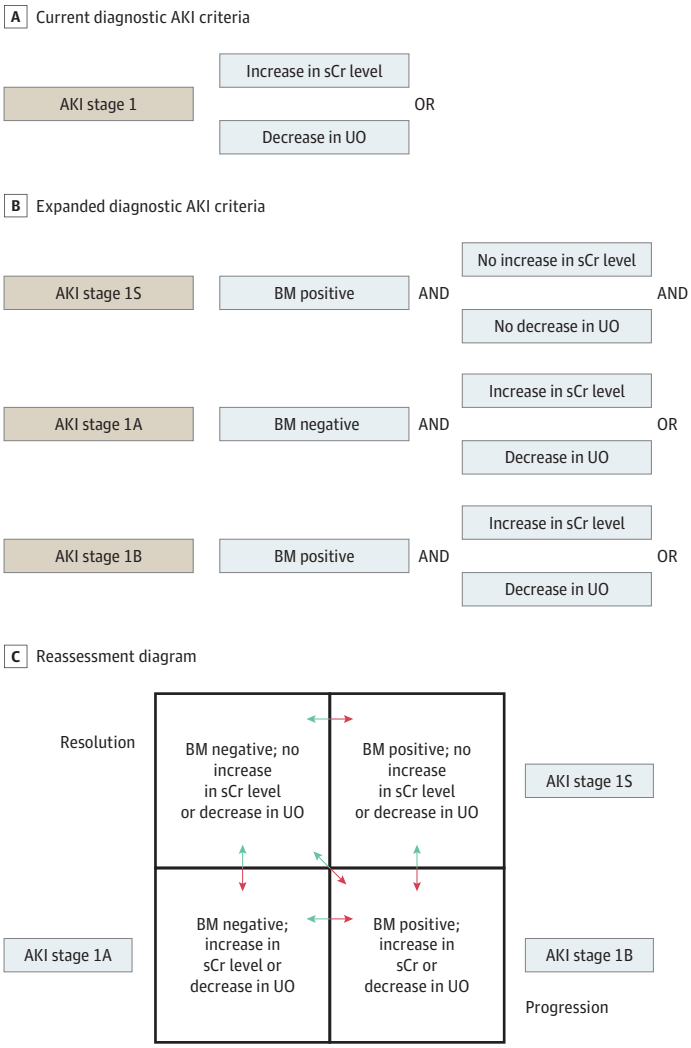
Consensus Statement 6

We suggest that a combination of damage and functional biomarkers, along with clinical information, be used to improve the diagnostic accuracy of AKI, to recognize the different pathophysiological processes, to discriminate AKI etiology, and to assess AKI severity. This recommendation received a grade of B, conditional.

The discovery of specific biomarkers of kidney injury has enabled a more precise delineation of the pathophysiology, site, mechanisms, and severity of injury[64,65] (Table). Some patients with positive damage biomarkers do not fulfill traditional AKI criteria yet have worse outcomes.[23] We propose that clinical information enriched by damage and functional biomarkers could lead to more sensitive AKI definitions. We therefore suggest a modification of KDIGO stage 1 AKI to reflect 3 substages (ie, 1S, 1A, and 1B) and to subcategorize stages 2 and 3 AKI by presence of biomarkers (**Figure 1** and **Figure 2**). Stage 1S identifies an early stage when there is evidence of kidney injury that is not detected by creatinine and urine output criteria. For example, in 345 children undergoing cardiopulmonary bypass,[25] the combination of functional (cystatin C) and damage (neutrophil gelatinase–associated lipocalin [NGAL]) biomarkers was superior to sCr in predicting the severity and

persistence of AKI. More recently, a study of 178 children[41] showed that those with elevated urine NGAL (uNGAL) concentrations without increased sCr levels had an almost 4-fold increased risk of all-stage AKI on day 3 compared with those without an uNGAL and sCr increase (uNGAL negative and sCr negative). Similarly, compared with patients who had no increase in uNGAL concentrations but

Figure 1. Refined Staging System for the Diagnosis of Acute Kidney Injury (AKI)



Patients with a biomarker (BM) of injury positivity without increase or decrease in serum creatinine (sCr) level and not reaching urine output (UO) criteria should be classified as stage 1S. Reassessment should be performed according to patient clinical context and temporal trends. Patients reaching SCr and UO criteria with no increase on BM are defined as stage 1A, and those reaching SCr and UO criteria with increased BM are reclassified as stage 1B. BM positivity should be based on its mechanism and defined threshold. Reprinted from Acute Disease Quality Initiative 23 and used with permission.

Figure 2. Proposed New Definition of Acute Kidney Injury

Functional criteria	Stage	Damage criteria
No change or sCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of sCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of sCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of sCr level by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

Functional markers include serum creatinine (sCr) and urine output (UO) but new functional markers may also be included. Reprinted from Acute Disease Quality Initiative 23 and used with permission. To convert sCr to millimoles per liter, multiply by 88.4. KRT indicates kidney replacement therapy.

an increase in sCr levels, patients who had uNGAL and sCr increases had a 12-fold increased risk of AKI stage 2 or 3 on day 3.

TIMP-2 and IGFBP7 have also been shown to improve risk stratification in critically ill patients with AKI stage 1.[14] Evaluation of longer-term outcomes demonstrated that the associated risks of TIMP-2 × IGFBP7 of greater than 2.0 $(ng/mL)^2/1000$ were equivalent to AKI progression even in instances in which no progression from AKI stage 1 was seen based on sCr and urine output. The ability to recognize the various pathophysiological processes mediating AKI will likely be critical in developing targeted therapies and designing pharmacological trials.[38,66]

Consensus Statement 7

We suggest that a combination of biomarkers may assist the planning of therapy and management of AKI. This recommendation received a grade of C, conditional.

Uncertainty regarding when kidney injury actually occurred is common. Biomarkers may be able to provide guidance in determining the onset and presence of kidney damage so that potential therapies can be initiated before the injury becomes irreversible[67] (eFigure 2 in the Supplement). Multiple biomarkers have the potential to shed light on the pathophysiology and provide an early detection system superior to creatinine.[36,68]

Biomarker-guided algorithms and goal-directed management protocols appear to provide benefit in preventing and/or mitigating AKI.[21,22,56,69,70] For instance, if biomarkers indicate kidney stress before permanent damage occurs, there is the possibility of reversing AKI[21,22] (eFigure 2 in the Supplement). Consequently, embedding biomarkers within goal-directed management protocols has the potential to affect AKI recovery.[70]

Consensus Statement 8

Inclusion of biomarker data with clinical assessments can be used to identify patients who will need KRT and facilitate optimal timing of KRT initiation. The recommendation received a grade of C, conditional.

Currently, the decision to start KRT is based on clinical judgement and conventional criteria. Several studies have evaluated different biomarkers in predicting the need for KRT with variable results.[34] In a meta-analysis of more than 15 000 patients,[34] the pooled AUROCs for urine and blood NGAL for prediction of KRT were 0.72 (95% CI, 0.64-0.80) and 0.76 (95% CI, 0.71-0.80), respectively, while sCr and cystatin C had pooled AUROCs of 0.76 (95% CI, 0.73-0.80) and 0.77 (95% CI, 0.73-0.81), respectively. Urine biomarkers interleukin-18, cystatin C, and TIMP-2 × IGFBP7 showed pooled AUROCs of 0.67 (95% CI, 0.61-0.73), 0.72 (95% CI, 0.58-0.87), and 0.86 (95% CI, 0.79-0.93), respectively.[34] Some limitations for biomarker-based predictions are the variable cutoffs, the reliance on single measurements, and confounding by underlying comorbidities and clinical conditions.

The furosemide stress test (FST) has been proposed as a means to predict the need for KRT after kidney transplantation and in patients with AKI.[71,72] Clinical risk scores predicting KRT are available for specific situations, ie, after cardiac surgery, but biomarkers of kidney damage have not been incorporated. In patients receiving mechanical ventilation, sCr combined with normalized urine NGAL (nuNGAL) and serum cystatin C combined with either nuNGAL or uNGAL were found to be the best predictors for KRT initiation (AUROC = 0.80).[40] Among patients without AKI on intensive care unit admission, the combination of serum cystatin C and Acute Physiology and Chronic Health Evaluation score performed best (AUROC = 0.78). In 2 randomized clinical trials, plasma NGAL failed to enrich the prediction for early KRT initiation.[46,73] Future studies should incorporate sequential assessments of both functional and damage biomarkers in patients identified as having high risk for needing KRT based on clinical risk scores.

Most studies evaluating the role of biomarkers to guide KRT discontinuation have relied on urine output, urinary Cr, or urea clearance.[74] The FST has also been shown to predict discontinuation of KRT (AUROC = 0.84).[75] An observational study[33] explored the role of serum cystatin C and NGAL in

110 patients at the time of cessation of continuous renal replacement therapy (CRRT). Patients who successfully discontinued CRRT had lower serum cystatin C levels and higher urine output at CRRT cessation than those who had to restart KRT. However, sCr and NGAL levels were not significantly lower in the group that recovered compared with patients in whom CRRT was restarted. Another study of 110 critically ill patients on CRRT[27] showed that serum NGAL was predictive of successful discontinuation of CRRT in patients with AKI but no sepsis whereas urine output was a significant predictor in patients with AKI with sepsis. Collective data suggest that there is currently limited evidence to support the use of any individual biomarker for predicting successful KRT cessation.

Biomarkers to Assess AKI Progression and Kidney Recovery

Studies have found that complete and sustained reversal of AKI episodes within 48 to 72 hours of onset was associated with better outcomes than persistent AKI; however, different definitions for persistent AKI were applied.[76] Thus the ADQI 16 working group proposed defining persistent AKI as AKI that lasts more than 48 hours and recommended the use of biomarkers to risk stratify patients for whom additional workup and evaluation might be warranted.[77]

Consensus Statement 9

We suggest that novel biomarkers can be used for prediction of duration and recovery of AKI. This recommendation received a grade of C, weak.

Among patients with community-acquired pneumonia enrolled in the Genetic and Inflammatory Markers of Sepsis cohort,[42] the predictive value of plasma NGAL concentrations on day 1 on kidney recovery was investigated in 181 patients with severe AKI. Recovery was defined as being alive and not requiring KRT at hospital discharge. Plasma NGAL alone predicted nonrecovery of kidney function (AUROC = 0.74). However, when compared with a clinical model, plasma NGAL did not augment risk prediction.

The performance of plasma proenkephalin-A was evaluated in 956 patients with sepsis who were enrolled in the multicenter Albumin Italian Outcome Sepsis trial.[26] Among the subgroup of 255 patients with a sCr level of 2.0mg/dL (to convert to millimoles per liter, multiply by 88.4) on the first day, 31% had an improvement in kidney function within 48 hours. Median (interquartile range) sCr level on day 1 was significantly lower in patients who recovered kidney function within 48 hours compared with those who did not recover (2.9 [2.5-3.3] mg/dL vs 3.2 [2.6-4.2] mg/dL; $P = .006$). Their median (interquartile range) day 1 plasma proenkephalin-A concentration was also significantly lower (137 [89-188] pmol/L) compared with patients without kidney recovery (226 [145-352] pmol/L). A study in patients with septic AKI[31] showed significantly higher proenkephalin-A concentrations in patients with major adverse kidney events, patients with persistent AKI, and those who had worsening of kidney function. The increase in proenkephalin-A concentrations preceded elevation of sCr levels in patients with worsening kidney function. A 2020 study of 331 critically ill patients with AKI stage 2 or 3 demonstrated that urinary C-C motif chemokine ligand 14 was predictive of persistent AKI.[5] Finally, in 733 patients undergoing cardiac surgery,[9] preoperative ratio of urinary dickkopf-3 to creatinine concentrations greater than 471 pg/mg was associated with a significantly higher risk of persistent kidney dysfunction (odds ratio, 6.67; 95% CI, 1.67-26.61; $P = .007$) and dialysis dependency (odds ratio, 13.57; 95% CI, 1.50-122.77; $P = .02$) after 90 days compared with a ratio of 471 pg/mg or less.[9]

Consensus Statement 10

Currently there is insufficient evidence to recommend the routine use of novel biomarkers to refine acute kidney disease (AKD) staging. This recommendation received a grade of C, strong.

AKD describes acute or subacute damage and/or loss of kidney function for a duration as long as 90 days[77] (**Figure 3**). To date, no study has evaluated the predictive value of novel biomarkers for AKD staging and subsequent outcomes.

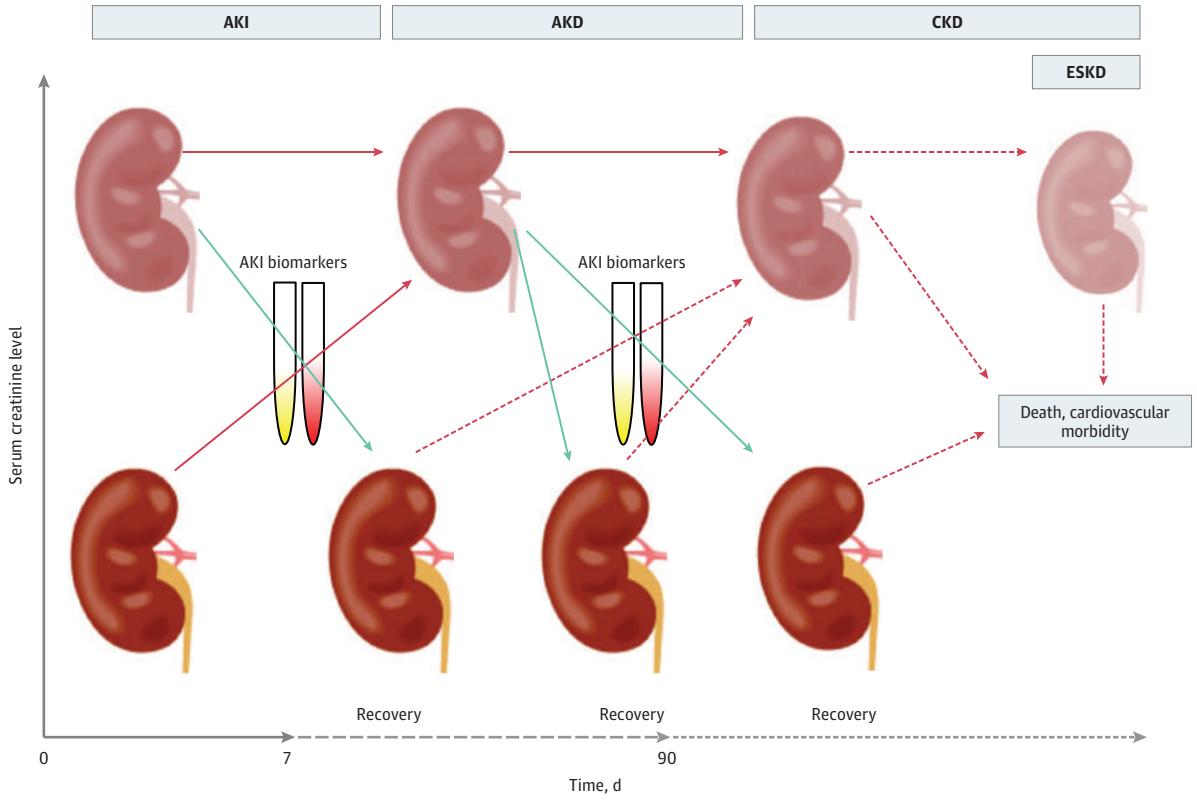
Consensus Statement 11

We recommend that biomarkers predictive of CKD staging and progression be incorporated into a comprehensive post-AKI/AKD care bundle and KHA. This recommendation received a grade of C, strong.

Studies have evaluated the long-term prognostic value of biomarkers for predicting KRT dependence and death among critically ill patients with AKI. Serum creatinine has a very limited role as a biomarker for kidney function in patients receiving KRT. A study using the Biological Markers of Recovery for the Kidney cohort[78] found increased concentrations of plasma interleukin (IL) 8 and IL-18 and tumor necrosis factor receptor type 1 (TNFR-I) on day 1 were independently associated with slower kidney recovery by day 60 among critically ill patients treated with KRT. In an analysis of multiple markers simultaneously,[78] increased IL-8 and TNFR-I in combination were associated with slower recovery and increased IL-8, migration inhibitory factor, and TNFR-I concentrations were associated with mortality. Using the same cohort, higher day 8 concentrations of plasma IL-6, IL-8, IL-18, IL-10, TNFR-I, and TNFR-II were associated with lower kidney recovery, and plasma concentrations of IL-6, IL-8, IL-10, IL-18, migration inhibitory factor, TNFR-I, and death receptor 5 were associated with mortality among patients receiving KRT.[78]

Another study[44] evaluated serum osteopontin, IL-6, and cystatin C for kidney recovery among 102 patients with AKI requiring KRT. Lower levels of osteopontin and IL-6 were associated with greater odds of 60-day survival with AUROCs of 0.81 and 0.74, respectively. The AUROC value for predicting survival reached its highest level when all biomarkers were combined with urine output and urinary and serum sCr upon discontinuation of KRT (AUROC = 0.88).

Figure 3. Transition From Acute Kidney Injury (AKI) to Recovery, Acute Kidney Disease (AKD), or Chronic Kidney Disease (CKD)



Biomarkers of kidney damage and function can refine the prediction of rapid recovery (ie, transient AKI) or persistent AKI. AKD is assessed between 7 and 90 days after an acute event. Prior to day 7, AKI criteria may still be reached, and after 90 days, CKD criteria are applicable. Scarce data suggest that new biomarkers of kidney damage and function can refine the prediction of pour outcomes (ie, death, chronic kidney disease) at intensive care unit discharge compared to serum creatinine. Reprinted from Acute Disease Quality Initiative 23 used with permission. ESKD indicates end-stage kidney disease.

In patients receiving KRT, a higher cystatin C value at discontinuation of KRT was independently predictive of chronic dialysis.[45] Urinary concentrations of TIMP-2 × IGFBP7 of greater than 0.3 $(ng/mL)^2/1000$, compared with 0.3 $(ng/mL)^2/1000$, have also been shown to be associated with death or KRT in patients with AKI (hazard ratio, 2.16; 95% CI, 1.32-3.53).[37] More recently, the FROG-ICU study evaluated the prognostic utility of different AKI biomarkers obtained at intensive care unit discharge on 1-year outcome in 1207 intensive care unit survivors.[19] Of 460 patients with AKI, 58 patients (12.6%) were identified as having AKD at intensive care unit discharge. Most patients with AKI in the intensive care unit had elevated biomarkers of kidney damage at discharge even with apparent recovery based on sCr level. However, the predictive value for 1-year mortality was only modest (AUROC range, 0.61-0.70).

Discussion

We have provided recommendations for the use of AKI biomarkers in routine clinical practice. However, there are still a substantial number of knowledge gaps that need to be covered in future studies (**Box**).

Box. Research Recommendations

1. Studies need to be performed to determine whether novel AKI biomarkers offer additional benefit in assessment of AKI risk prior to a planned nephrotoxic exposure.
2. Appropriate performance of candidate biomarkers should be evaluated for optimal results of preventive measures guided by biomarkers, in particular:
   a. the role of damage biomarkers to prevent AKI after specific exposures (ie, drugs) needs further investigation;
   b. the cost-effectiveness of using biomarkers to predict and prevent AKI needs further evaluation; and
   c. the time course, cutoffs, and interactions between functional and damage biomarkers of AKI should be further assessed.
3. Studies should investigate the role of single vs serial measurements of biomarkers in the prediction of AKI and the impact of preventive measures.
4. Research is necessary to investigate the role of nonkidney biomarkers (eg, procalcitonin, natriuretic peptide, troponin) to identify patient populations at risk for AKI.
5. We suggest further research on whether a combination of validated biomarkers can help improve the detection of etiology and the management of AKI.
6. We suggest further research on how the inherent characteristics of biomarkers (including temporal patterns) affect the understanding of the process leading to AKI, its complications, and recovery.
7. Investigations should focus on determining whether a change in serum creatinine/oliguria without change of damage biomarker is associated with worse kidney and patient outcomes.
8. Investigations should focus on determining whether elevation in biomarkers without any changes in serum creatinine/oliguria is associated with worse kidney and patient outcomes.
9. The role of serial biomarker testing should be compared with real-time glomerular filtration rate measurement.
10. Future studies are needed to evaluate the combination of damage and functional biomarkers with clinical assessments to determine the risk profiles of patients who may need kidney replacement therapy.
11. Research is needed to evaluate the utility of dynamic assessment of functional and structural markers correlated with clinical data to define the optimal timing for initiating and stopping kidney replacement therapy.
12. Studies have identified a number of candidate biomarkers and diagnostics for persistent AKI and kidney recovery. We recommend prospective validation of these novel biomarkers for prediction of persistent AKI and kidney recovery. These biomarkers should also be evaluated for their ability to improve patient management alone or in combination.
13. We recommend prospective validation of candidate biomarkers for acute kidney disease staging and prognosis and to predict successful kidney replacement therapy discontinuation.
14. We recommend prospective validation of candidate biomarkers, in combination with clinical assessment tools for the prediction of chronic kidney disease staging and longer-term outcomes after AKI or acute kidney disease.

Abbreviation: AKI, acute kidney injury.

Limitations

This study has limitations. Our recommendations are based on existing evidence and consensus but we did not perform a systematic review of all individual studies. We also acknowledge that further biomarker studies are in progress or have been completed since the ADQI meeting was held and that it is possible that the results would affect our recommendations.

Conclusions

Considerable progress has been made in the field of AKI biomarkers, which has resulted in a better understanding of the pathophysiology of AKI and improved outcomes with biomarker-guided management. Our consensus recommendations based on existing data aim to assist clinicians at the bedside. We acknowledge that the current literature contains some bias and limitations, and further research is needed. However, the prospect of clearer identification of high-risk patients and different AKI subphenotypes and the integration of appropriately selected biomarkers in routine clinical practice hold the key to further improvement in AKI care.

ARTICLE INFORMATION

Accepted for Publication: July 3, 2020.

Published: October 6, 2020. doi:10.1001/jamanetworkopen.2020.19209

Correction: This article was corrected on November 10, 2020, to fix errors in the byline and affiliations.

Corresponding Author: Marlies Ostermann, MD, Department of Critical Care and Nephrology, King's College London, Guy's and St Thomas' Hospital, London, United Kingdom (marlies.ostermann@gstt.nhs.uk).

Author Affiliations: Department of Critical Care and Nephrology, King's College London, Guy's and St Thomas' Hospital, London, United Kingdom (Ostermann); Department of Anaesthesiology, Intensive Care Medicine, and Pain Medicine, University Hospital Münster, Münster, Germany (Zarbock); Center for Acute Care Nephrology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio (Goldstein); Division of Pulmonary and Critical Care Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota (Kashani); Division of Nephrology, Department of Medicine, University of California, San Diego (Macedo); Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania (Murugan, Kellum); Department of Perioperative Medicine and Intensive Care Medicine, Karolinska University Hospital, Stockholm, Sweden (Bell); Intensive Care Unit, Royal Surrey Hospital NHS Foundation Trust, Surrey, United Kingdom (Forni); Department of Critical Care Medicine, AdventHealth Waterman, Orlando, Florida (Guzzi); Division of Intensive Care and Emergency Medicine, Department of Internal Medicine, Medical University of Innsbruck, Innsbruck, Austria (Joannidis); Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy, Pittsburgh, Pennsylvania (Kane-Gill); Department of Anesthesia and Perioperative Care, University of California, San Francisco (Legrand); Department of Medicine, UCSD Medical Center, University of California, San Diego (Mehta); School of Medicine, University College Dublin, Dublin, Ireland (Murray); Department of Intensive Care Medicine, Nijmegen Medical Center, Radboud University, Nijmegen, the Netherlands (Pickkers); Department of Laboratory Medicine, University Hospital of Padova, Padova, Italy (Plebani); Department of Medicine—DIMED, University of Padova, Padova, Italy (Plebani); William Harvey Research Institute, Royal London Hospital, Queen Mary University of London, London, United Kingdom (Prowle); Pediatric Cardiac Intensive Care Unit, Bambino Gesu Children's Hospital, Istituto Di Ricovero e Cura a Carattere Scientifico, Rome, Italy (Ricci); Anesthesiology and Intensive Care Medicine, Edouard Herriot Hospital, Lyon, France (Rimmelé); Division of Nephrology, University of Virginia Health System, Charlottesville (Rosner); Department of Anesthesiology and Pain Medicine, University of Alberta, Edmonton, Alberta, Canada (Shaw); Department of Medicine, University of Padova, Padova, Italy (Ronco); Department of Nephrology, Dialysis, and Transplantation, International Renal Research Institute, San Bortolo Hospital, Vicenza, Italy (Ronco); Division of Nephrology Hypertension, Department of Medicine, Mayo Clinic, Rochester, Minnesota (Kashani); Department of Clinical and Experimental Medicine, Faculty of Health Sciences, University of Surrey, Surrey, United Kingdom (Forni).

Author Contributions: Drs Ostermann and Zarbock had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Ostermann and Zarbock are co–first authors. Drs Kellum and Ronco are co–senior authors.

Concept and design: Ostermann, Zarbock, Goldstein, Kashani, Macedo, Bell, Forni, Guzzi, Joannidis, Kane-Gill, Legrand, Mehta, Murray, Pickkers, Plebani, Prowle, Rimmelé, Rosner, Shaw, Kellum, Ronco.

Acquisition, analysis, or interpretation of data: Ostermann, Zarbock, Murugan, Bell, Forni, Joannidis, Kane-Gill, Legrand, Murray, Plebani, Ricci, Rimmelé, Rosner, Shaw, Kellum, Ronco.

Drafting of the manuscript: Ostermann, Zarbock, Goldstein, Kashani, Macedo, Murugan, Bell, Forni, Guzzi, Joannidis, Kane-Gill, Legrand, Mehta, Murray, Plebani, Prowle, Ricci, Rimmelé, Rosner, Shaw.

Critical revision of the manuscript for important intellectual content: Ostermann, Zarbock, Kashani, Macedo, Murugan, Bell, Forni, Guzzi, Joannidis, Kane-Gill, Legrand, Mehta, Murray, Pickkers, Plebani, Prowle, Rimmelé, Rosner, Shaw, Kellum, Ronco.

Obtained funding: Zarbock, Mehta, Kellum.

Administrative, technical, or material support: Ostermann, Zarbock, Macedo, Bell, Forni, Guzzi, Murray, Rimmelé, Rosner, Shaw, Kellum.

Supervision: Ostermann, Zarbock, Goldstein, Murugan, Bell, Mehta, Murray, Rosner, Shaw, Ronco.

Conflict of Interest Disclosures: Dr Ostermann reported receiving grants from BioMerieux, Baxter, and BioPorto and speaker honoraria from BioMerieux outside the submitted work. Dr Zarbock reported receiving grants and personal fees from Baxter, Astute Medical, and Fresenius; grants from Astellas, Deutsche Forschungsgesellschaft, Bundesministerium fuer Bildung und Forschung, and Else Kriener-Fresenius-Stiftung; and personal fees from Amomed, Ratiopharm, BioMerieux, AM Pharma, Springer, and *Anaesthesia and Analgesia* during the conduct of the study as well as receiving grants from Deutsche Forschungsgesellschaft, Else Kroener-Fresenius-Stiftung, and Astellas; grants and personal fees from Baxter, Fresenius, and Astute Medical; and personal fees from AM Pharma, BioMerieux, Amomed, Springer, and *Anaesthesia and Analgesia* outside the submitted work. Dr Goldstein reported receiving personal fees from MediBeacon and grants and personal fees from BioPorto outside the submitted work. Dr Kashani reported receiving grants from Astute Medical during the conduct of the study. Dr Bell reported having an investigator-initiated research grant from Baxter. Dr Forni reported receiving personal fees from Astute Medical and BioMerieux; receiving research funding from Baxter and Ortho-Clinical-Diagnostics; and receiving speaker or consultant honoraria from Fresenius, Exthera, Baxter, and Astute Medical. Dr Guzzi reported being a speaker for BioMerieux outside the submitted work. Dr Joannidis reported receiving grants from Baxter; grants and personal fees from Fresenius Kabi; and speaking and/or consulting honoraria from Sphingotec, CLS-Behring, Fresenius and Astute Medical outside the submitted work. Dr Legrand reported receiving research support from Sphingtotec during the conduct of the study as well as consulting fees from Novaritis and speaking fees from Fresenius and Baxter outside the submitted work. Dr Mehta reported serving on the advisory boards of BioMerieux, Baxter, and Sphingotec; serving on the steering committee of AM Pharma; receiving research funding from Fresenius Medical and Fresenius Kabi; and consulting for Baxter, AM Pharma, Intercept, BioMerieux, Sanofi, GE Healthcare, Indalo, Sphingotec, and Mallinckrodt outside the submitted work. Dr Murray reported receiving personal fees from FAST Biomedical, AM Pharma, Renibus Therapeutics, and Sphingotec outside the submitted work. Dr Murugan reported receiving grants from the National Institute of Diabetes and Digestive and Renal Diseases outside the submitted work. Dr Pickkers reported receiving travel and consultation honoraria from AM Pharma, Sphingotec, Adrenomed, Exponential Biotherapies, and Baxter outside the submitted work. Dr Prowle reported receiving personal fees from Nikkiso Europe, Baxter, Fresenius, MediBeacon, Quark Pharma, and BioMerieux; receiving funding from BioMerieux; and serving as a consultant with MediBeacon, Quark Pharma, GE Healthcare, and Nikkiso Europe outside the submitted work. Dr Rimmelé reported receiving personal fees from BioMerieux during the conduct of the study as well as grants and personal fees from Baxter, personal fees from Fresenius, and personal fees from Braun outside the submitted work. Dr Shaw reported receiving personal fees from Edwards Lifesciences, FAST Biomedical, Astellas, and Renibus Therapeutics outside the submitted work. Dr Kellum reported receiving grants and personal fees from Astute Medical and BioMerieux during the conduct of the study and grants and personal fees from Fresenius, Potrero, and RenalSense outside the submitted work. Dr Ronco reported serving on the advisory board of Baxter, writing papers for GE, receiving speaking fees from Cytosorbents and Jafron, consulting with Medtronic and Asahi Kasei Medical Co, belonging to the speakers bureau for Ortho-Clinical-Diagnostics, and serving on the advisory board of BioMerieux outside the submitted work. No other disclosures were reported.

Funding/Support: The face-to-face meeting was supported by educational grants from Baxter, Nxstage, Astute Medical, Sphingotec, Cytosorbents, and Bioporto.

Role of the Funder/Sponsor: The funders had no involvement in the selection of the panelists, design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or

approval of the manuscript; and decision to submit the manuscript for publication. Representatives were present at the face-to-face meeting but did not participate in the panel discussions, voting, or final decisions.

Additional Information: Panelists received travel reimbursement but no honoraria.

REFERENCES

1. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Sppl*. 2012;2(1):1-138. doi:10.1038/kisup.2012.1

2. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. *Kidney Int*. 2008;73(9):1008-1016. doi:10.1038/sj.ki.5002729

3. Charlton JR, Portilla D, Okusa MD. A basic science view of acute kidney injury biomarkers. *Nephrol Dial Transplant*. 2014;29(7):1301-1311. doi:10.1093/ndt/gft510

4. Heller F, Frischmann S, Grünbaum M, Zidek W, Westhoff TH. Urinary calprotectin and the distinction between prerenal and intrinsic acute kidney injury. *Clin J Am Soc Nephrol*. 2011;6(10):2347-2355. doi:10.2215/CJN.02490311

5. Hoste E, Bihorac A, Al-Khafaji A, et al; RUBY Investigators. Identification and validation of biomarkers of persistent acute kidney injury: the RUBY study. *Intensive Care Med*. 2020;46(5):943-953. doi:10.1007/s00134-019-05919-0

6. De Loor J, Decruyenaere J, Demeyere K, Nuytinck L, Hoste EA, Meyer E. Urinary chitinase 3-like protein 1 for early diagnosis of acute kidney injury: a prospective cohort study in adult critically ill patients. *Crit Care*. 2016;20:38. doi:10.1186/s13054-016-1192-x

7. Ho J, Tangri N, Komenda P, et al. Urinary, plasma, and serum biomarkers' utility for predicting acute kidney injury associated with cardiac surgery in adults: a meta-analysis. *Am J Kidney Dis*. 2015;66(6):993-1005. doi:10.1053/j.ajkd.2015.06.018

8. Ravn B, Rimes-Stigare C, Bell M, et al. Creatinine versus cystatin C based glomerular filtration rate in critically ill patients. *J Crit Care*. 2019;52:136-140. doi:10.1016/j.jcrc.2019.04.007

9. Schunk SJ, Zarbock A, Meersch M, et al. Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study. *Lancet*. 2019;394(10197):488-496. doi:10.1016/S0140-6736(19)30769-X

10. Koyner JL, Vaidya VS, Bennett MR, et al. Urinary biomarkers in the clinical prognosis and early detection of acute kidney injury. *Clin J Am Soc Nephrol*. 2010;5(12):2154-2165. doi:10.2215/CJN.00740110

11. Vaidya VS, Waikar SS, Ferguson MA, et al. Urinary biomarkers for sensitive and specific detection of acute kidney injury in humans. *Clin Transl Sci*. 2008;1(3):200-208. doi:10.1111/j.1752-8062.2008.00053.x

12. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17(1):R25. doi:10.1186/cc12503

13. Ostermann M, McCullough PA, Forni LG, et al; all SAPPHIRE Investigators. Kinetics of urinary cell cycle arrest markers for acute kidney injury following exposure to potential renal insults. *Crit Care Med*. 2018;46(3):375-383. doi:10.1097/CCM.0000000000002847

14. Joannidis M, Forni LG, Haase M, et al; Sapphire Investigators. Use of cell cycle arrest biomarkers in conjunction with classical markers of acute kidney injury. *Crit Care Med*. 2019;47(10):e820-e826. doi:10.1097/CCM.0000000000003907

15. Fan PC, Chen CC, Peng CC, et al. A circulating miRNA signature for early diagnosis of acute kidney injury following acute myocardial infarction. *J Transl Med*. 2019;17(1):139. doi:10.1186/s12967-019-1890-7

16. Moledina DG, Isguven S, McArthur E, et al; Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury (TRIBE-AKI) Consortium. Plasma monocyte chemotactic protein-1 is associated with acute kidney injury and death after cardiac operations. *Ann Thorac Surg*. 2017;104(2):613-620. doi:10.1016/j.athoracsur.2016.11.036

17. Ramesh G, Krawczeski CD, Woo JG, Wang Y, Devarajan P. Urinary netrin-1 is an early predictive biomarker of acute kidney injury after cardiac surgery. *Clin J Am Soc Nephrol*. 2010;5(3):395-401. doi:10.2215/CJN.05140709

18. Lorenzen JM, Hafer C, Faulhaber-Walter R, et al. Osteopontin predicts survival in critically ill patients with acute kidney injury. *Nephrol Dial Transplant*. 2011;26(2):531-537. doi:10.1093/ndt/gfq498

19. Legrand M, Hollinger A, Vieillard-Baron A, et al; French and euRopean Outcome reGistry in ICUs (FROG-ICU) Investigators. One-year prognosis of kidney injury at discharge from the ICU: a multicenter observational study. *Crit Care Med*. 2019;47(12):e953-e961. doi:10.1097/CCM.0000000000004010

20. Murray PT, Mehta RL, Shaw A, et al; ADQI 10 workgroup. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. *Kidney Int*. 2014;85(3):513-521. doi:10.1038/ki.2013.374

21. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med*. 2017;43(11):1551-1561. doi:10.1007/s00134-016-4670-3

22. Göcze I, Jauch D, Götz M, et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. *Ann Surg*. 2018;267(6):1013-1020. doi:10.1097/SLA.0000000000002485

23. Haase M, Devarajan P, Haase-Fielitz A, et al. The outcome of neutrophil gelatinase-associated lipocalin-positive subclinical acute kidney injury: a multicenter pooled analysis of prospective studies. *J Am Coll Cardiol*. 2011;57(17):1752-1761. doi:10.1016/j.jacc.2010.11.051

24. Kellum JA, Bellomo R, Ronco C. Acute Dialysis Quality Initiative (ADQI): methodology. *Int J Artif Organs*. 2008;31(2):90-93. doi:10.1177/039139880803100202

25. Basu RK, Wong HR, Krawczeski CD, et al. Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery. *J Am Coll Cardiol*. 2014;64(25):2753-2762. doi:10.1016/j.jacc.2014.09.066

26. Caironi P, Latini R, Struck J, et al; ALBIOS Study Investigators. Circulating proenkephalin, acute kidney injury, and its improvement in patients with severe sepsis or shock. *Clin Chem*. 2018;64(9):1361-1369. doi:10.1373/clinchem.2018.288068

27. Chen X, Chen Z, Wei T, Li P, Zhang L, Fu P. The effect of serum neutrophil gelatinase-associated lipocalin on the discontinuation of continuous renal replacement therapy in critically ill patients with acute kidney injury. *Blood Purif*. 2019;48(1):10-17. doi:10.1159/000499026

28. Engelman DT, Crisafi C, Germain M, et al. Using urinary biomarkers to reduce acute kidney injury following cardiac surgery. *J Thorac Cardiovasc Surg*. 2019;S0022-5223(19)32245-7. doi:10.1016/j.jtcvs.2019.10.034

29. Grams ME, Astor BC, Bash LD, Matsushita K, Wang Y, Coresh J. Albuminuria and estimated glomerular filtration rate independently associate with acute kidney injury. *J Am Soc Nephrol*. 2010;21(10):1757-1764. doi:10.1681/ASN.2010010128

30. Hodgson LE, Venn RM, Short S, et al. Improving clinical prediction rules in acute kidney injury with the use of biomarkers of cell cycle arrest: a pilot study. *Biomarkers*. 2019;24(1):23-28. doi:10.1080/1354750X.2018.1493617

31. Hollinger A, Wittebole X, François B, et al. Proenkephalin A 119-159 (Penkid) is an early biomarker of septic acute kidney injury: the Kidney in Sepsis and Septic Shock (Kid-SSS) Study. *Kidney Int Rep*. 2018;3(6):1424-1433. doi:10.1016/j.ekir.2018.08.006

32. Husain-Syed F, Ferrari F, Sharma A, et al. Preoperative renal functional reserve predicts risk of acute kidney injury after cardiac operation. *Ann Thorac Surg*. 2018;105(4):1094-1101. doi:10.1016/j.athoracsur.2017.12.034

33. Kim CS, Bae EH, Ma SK, Kim SW. A prospective observational study on the predictive value of serum cystatin C for successful weaning from continuous renal replacement therapy. *Kidney Blood Press Res*. 2018;43(3):872-881. doi:10.1159/000490335

34. Klein SJ, Brandtner AK, Lehner GF, et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Intensive Care Med*. 2018;44(3):323-336. doi:10.1007/s00134-018-5126-8

35. Kane-Gill SL, Peerapornratana S, Wong A, et al. Use of tissue inhibitor of metalloproteinase 2 and insulin-like growth factor binding protein 7 [TIMP2]•[IGFBP7] as an AKI risk screening tool to manage patients in the real-world setting. *J Crit Care*. 2020;57:97-101. doi:10.1016/j.jcrc.2020.02.002

36. Koyner JL, Garg AX, Coca SG, et al; TRIBE-AKI Consortium. Biomarkers predict progression of acute kidney injury after cardiac surgery. *J Am Soc Nephrol*. 2012;23(5):905-914. doi:10.1681/ASN.2011090907

37. Koyner JL, Shaw AD, Chawla LS, et al; Sapphire Investigators. Tissue inhibitor metalloproteinase-2 (TIMP-2) ·IGF-binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI. *J Am Soc Nephrol*. 2015;26(7):1747-1754. doi:10.1681/ASN.2014060556

38. Moledina DG, Wilson FP, Pober JS, et al. Urine TNF-α and IL-9 for clinical diagnosis of acute interstitial nephritis. *JCI Insight*. 2019;4(10):127456. doi:10.1172/jci.insight.127456

39. Murugan R, Wen X, Shah N, et al; Biological Markers for Recovery of Kidney (BioMaRK) Study Investigators. Plasma inflammatory and apoptosis markers are associated with dialysis dependence and death among critically ill patients receiving renal replacement therapy. *Nephrol Dial Transplant*. 2014;29(10):1854-1864. doi:10.1093/ndt/gfu051

40. Pipili C, Ioannidou S, Tripodaki ES, et al. Prediction of the renal replacement therapy requirement in mechanically ventilated critically ill patients by combining biomarkers for glomerular filtration and tubular damage. *J Crit Care*. 2014;29(4):692.e7-692.e13. doi:10.1016/j.jcrc.2014.02.011

41. Stanski N, Menon S, Goldstein SL, Basu RK. Integration of urinary neutrophil gelatinase-associated lipocalin with serum creatinine delineates acute kidney injury phenotypes in critically ill children. *J Crit Care*. 2019;53:1-7. doi:10.1016/j.jcrc.2019.05.017

42. Srisawat N, Murugan R, Lee M, et al; Genetic and Inflammatory Markers of Sepsis (GenIMS) Study Investigators. Plasma neutrophil gelatinase-associated lipocalin predicts recovery from acute kidney injury following community-acquired pneumonia. *Kidney Int*. 2011;80(5):545-552. doi:10.1038/ki.2011.160

43. Wahl TS, Graham LA, Morris MS, et al. Association between preoperative proteinuria and postoperative acute kidney injury and readmission. *JAMA Surg*. 2018;153(9):e182009. doi:10.1001/jamasurg.2018.2009

44. Yang T, Sun S, Zhao Y, et al. Biomarkers upon discontinuation of renal replacement therapy predict 60-day survival and renal recovery in critically ill patients with acute kidney injury. *Hemodial Int*. 2018;22(1):56-65. doi:10.1111/hdi.12532

45. Yang T, Sun S, Lin L, et al. Predictive factors upon discontinuation of renal replacement therapy for long-term chronic dialysis and death in acute kidney injury patients. *Artif Organs*. 2017;41(12):1127-1134. doi:10.1111/aor.12927

46. Zarbock A, Kellum JA, Schmidt C, et al. Effect of early vs delayed initiation of renal replacement therapy on mortality in critically ill patients with acute kidney injury: the ELAIN randomized clinical trial. *JAMA*. 2016;315(20):2190-2199. doi:10.1001/jama.2016.5828

47. Kashani K, Rosner MH, Haase M, et al. Quality improvement goals for acute kidney injury. *Clin J Am Soc Nephrol*. 2019;14(6):941-953. doi:10.2215/CJN.01250119

48. Shlipak MG, Mattes MD, Peralta CA. Update on cystatin C: incorporation into clinical practice. *Am J Kidney Dis*. 2013;62(3):595-603. doi:10.1053/j.ajkd.2013.03.027

49. Lewington AJ, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int*. 2013;84(3):457-467. doi:10.1038/ki.2013.153

50. Joslin J, Wilson H, Zubli D, et al. Recognition and management of acute kidney injury in hospitalised patients can be partially improved with the use of a care bundle. *Clin Med (Lond)*. 2015;15(5):431-436. doi:10.7861/clinmedicine.15-5-431

51. Basu RK, Kaddourah A, Goldstein SL; AWARE Study Investigators. Assessment of a renal angina index for prediction of severe acute kidney injury in critically ill children: a multicentre, multinational, prospective observational study. *Lancet Child Adolesc Health*. 2018;2(2):112-120. doi:10.1016/S2352-4642(17)30181-5

52. Chiofolo C, Chbat N, Ghosh E, Eshelman L, Kashani K. Automated continuous acute kidney injury prediction and surveillance: a random forest model. *Mayo Clin Proc*. 2019;94(5):783-792. doi:10.1016/j.mayocp.2019.02.009

53. Koyner JL, Adhikari R, Edelson DP, Churpek MM. Development of a multicenter ward-based AKI prediction model. *Clin J Am Soc Nephrol*. 2016;11(11):1935-1943. doi:10.2215/CJN.00280116

54. Koyner JL, Carey KA, Edelson DP, Churpek MM. The development of a machine learning inpatient acute kidney injury prediction model. *Crit Care Med*. 2018;46(7):1070-1077. doi:10.1097/CCM.0000000000003123

55. Malhotra R, Kashani KB, Macedo E, et al. A risk prediction score for acute kidney injury in the intensive care unit. *Nephrol Dial Transplant*. 2017;32(5):814-822. doi:10.1093/ndt/gfx026

56. Rizo-Topete LM, Rosner MH, Ronco C. Acute kidney injury risk assessment and the nephrology rapid response team. *Blood Purif*. 2017;43(1-3):82-88. doi:10.1159/000452402

57. Rimes-Stigare C, Ravn B, Awad A, et al. Creatinine- and cystatin C-based incidence of chronic kidney disease and acute kidney disease in AKI survivors. *Crit Care Res Pract*. 2018;2018:7698090. doi:10.1155/2018/7698090

58. Frazee EN, Rule AD, Herrmann SM, et al. Serum cystatin C predicts vancomycin trough levels better than serum creatinine in hospitalized patients: a cohort study. *Crit Care*. 2014;18(3):R110. doi:10.1186/cc13899

59. Frazee E, Rule AD, Lieske JC, et al. Cystatin C-guided vancomycin dosing in critically ill patients: a quality improvement project. *Am J Kidney Dis*. 2017;69(5):658-666. doi:10.1053/j.ajkd.2016.11.016

60. Barreto EF, Rule AD, Murad MH, et al. Prediction of the renal elimination of drugs with cystatin C vs creatinine: a systematic review. *Mayo Clin Proc*. 2019;94(3):500-514. doi:10.1016/j.mayocp.2018.08.002

61. Barreto EF, Rule AD, Voils SA, Kane-Gill SL. Innovative use of novel biomarkers to improve the safety of renally eliminated and nephrotoxic medications. *Pharmacotherapy*. 2018;38(8):794-803. doi:10.1002/phar.2149

62. Murray PT, Wettersten N, van Veldhuisen DJ, et al. Utility of urine neutrophil gelatinase-associated lipocalin for worsening renal function during hospitalization for acute heart failure: primary findings of the Urine N-gal Acute Kidney Injury N-gal Evaluation of Symptomatic Heart Failure Study (AKINESIS). *J Card Fail*. 2019;25(8):654-665. doi:10.1016/j.cardfail.2019.05.009

63. Mårtensson J, Martling CR, Bell M. Novel biomarkers of acute kidney injury and failure: clinical applicability. *Br J Anaesth*. 2012;109(6):843-850. doi:10.1093/bja/aes357

64. Singh R, Dodkins J, Doyle JF, Forni LG. Acute kidney injury biomarkers: what do they tell us? *Contrib Nephrol*. 2018;193:21-34. doi:10.1159/000484960

65. Endre ZH, Kellum JA, Di Somma S, et al. Differential diagnosis of AKI in clinical practice by functional and damage biomarkers: workgroup statements from the tenth Acute Dialysis Quality Initiative Consensus Conference. *Contrib Nephrol*. 2013;182:30-44. doi:10.1159/000349964

66. Okusa MD, Rosner MH, Kellum JA, Ronco C; Acute Dialysis Quality Initiative XIII Workgroup. Therapeutic targets of human AKI: harmonizing human and animal AKI. *J Am Soc Nephrol*. 2016;27(1):44-48. doi:10.1681/ASN.2015030233

67. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. *Clin Chem Lab Med*. 2017;55(8):1074-1089. doi:10.1515/cclm-2016-0973

68. Kane-Gill SL, Smithburger PL, Kashani K, Kellum JA, Frazee E. Clinical relevance and predictive value of damage biomarkers of drug-induced kidney injury. *Drug Saf*. 2017;40(11):1049-1074. doi:10.1007/s40264-017-0565-7

69. Berdugo MA, Kirson NY, Zimmer L, et al. Economic and clinical benefits of early identification of acute kidney injury using a urinary biomarker. *J Med Econ*. 2019;22(12):1281-1289. doi:10.1080/13696998.2019.1636053

70. Guzzi LM, Bergler T, Binnall B, et al. Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel. *Crit Care*. 2019;23(1):225. doi:10.1186/s13054-019-2504-8

71. McMahon BA, Koyner JL, Novick T, et al. The prognostic value of the furosemide stress test in predicting delayed graft function following deceased donor kidney transplantation. *Biomarkers*. 2018;23(1):61-69. doi:10.1080/1354750X.2017.1387934

72. Lumlertgul N, Peerapornratana S, Trakarnvanich T, et al; FST Study Group. Early versus standard initiation of renal replacement therapy in furosemide stress test non-responsive acute kidney injury patients (the FST trial). *Crit Care*. 2018;22(1):101. doi:10.1186/s13054-018-2021-1

73. Wald R, Adhikari NK, Smith OM, et al; Canadian Critical Care Trials Group. Comparison of standard and accelerated initiation of renal replacement therapy in acute kidney injury. *Kidney Int*. 2015;88(4):897-904. doi:10.1038/ki.2015.184

74. Schiffl H. Discontinuation of renal replacement therapy in critically ill patients with severe acute kidney injury: predictive factors of renal function recovery. *Int Urol Nephrol*. 2018;50(10):1845-1851. doi:10.1007/s11255-018-1947-1

75. van der Voort PH, Boerma EC, Pickkers P. The furosemide stress test to predict renal function after continuous renal replacement therapy. *Crit Care*. 2014;18(3):429. doi:10.1186/cc13871

76. Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD, Clermont G. Classifying AKI by urine output versus serum creatinine level. *J Am Soc Nephrol*. 2015;26(9):2231-2238. doi:10.1681/ASN.2014070724

77. Chawla LS, Bellomo R, Bihorac A, et al; Acute Disease Quality Initiative Workgroup 16. Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup. *Nat Rev Nephrol*. 2017;13(4):241-257. doi:10.1038/nrneph.2017.2

78. Murugan R, Wen X, Keener C, et al; Biological Markers of Recovery for the Kidney (BioMaRK) Study Investigators. Associations between intensity of RRT, inflammatory mediators, and outcomes. *Clin J Am Soc Nephrol*. 2015;10(6):926-933. doi:10.2215/CJN.04560514

SUPPLEMENT.

eTable 1. ADQI 23 Working Groups and Assignments
eTable 2. Selected Articles that Served as Evidence for the Recommendations
eTable 3. GRADE System Used for Consensus Statement Ratings
eFigure 1. Kidney Health Assessment
eFigure 2. Use of AKI Biomarkers During Course of AKI

Review

Weixuan Fan, Ghada Ankawi, Jingxiao Zhang, Kumar Digvijay, Davide Giavarina, Yongjie Yin* and Claudio Ronco

Current understanding and future directions in the application of TIMP-2 and IGFBP7 in AKI clinical practice

https://doi.org/10.1515/cclm-2018-0776
Received July 22, 2018; accepted August 2, 2018; previously published online September 4, 2018

Abstract: NephroCheck® is the commercial name of a combined product of two urinary biomarkers, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7), expressed as [TIMP-2] · [IGFBP7], used to identify patients at high risk of acute kidney injury (AKI). AKI is a common and harmful complication especially in critically-ill patients, which can induce devastating short- and long-term outcomes. Over the past decade, numerous clinical studies have evaluated the utility of several biomarkers (e.g. neutrophil gelatinase-associated lipocalin, interleukin-18, liver-type fatty acid binding protein and kidney injury molecule-1, cystatin C) in the early diagnosis and risk stratification of AKI. Among all these biomarkers, [TIMP-2] · [IGFBP7] was confirmed to be superior in early detection of AKI, before the decrease of renal function is evident. In 2014, the US Food and Drug Administration permitted marketing of NephroCheck® (Astute Medical) (measuring urinary [TIMP-2] · [IGFBP7]) to determine if certain critically-ill patients are at risk of developing moderate to severe AKI. It has since been applied to clinical work in many hospitals of the United States and Europe to improve the diagnostic accuracy and outcomes of AKI patients. Now, more and more research is devoted to the evaluation of its application value, meaning and method in different clinical settings. In this review, we summarize the current research status of [TIMP-2] · [IGFBP7] and point out its future directions.

Keywords: acute kidney injury (AKI); biomarker; cell cycle arrest; insulin-like growth factor-binding protein 7 (IGFBP7); NephroCheck®; tissue inhibitor of metalloproteinases-2 (TIMP-2).

***Corresponding author: Yongjie Yin,** Department of Emergency and Critical Care, The Second Hospital of Jilin University, Ziqiang Street No. 218, 130021 Changchun, P.R. China, E-mail: yinyongjie2003@sina.cn
Weixuan Fan and Jingxiao Zhang: Department of Emergency and Critical Care, The Second Hospital of Jilin University, Changchun, P.R. China; and International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy. https://orcid.org/0000-0002-9921-8194 (W. Fan)
Ghada Ankawi: International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; and Department of Internal Medicine and Nephrology, King Abdulaziz University, Jeddah, Saudi Arabia
Kumar Digvijay: International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; and Department of Nephrology and Research, Sir Ganga Ram Hospital, New Delhi, India
Davide Giavarina: Department of Clinical Chemistry and Hematology Laboratory, San Bortolo Hospital, Vicenza, Italy
Claudio Ronco: International Renal Research Institute of Vicenza (IRRIV), Vicenza, Italy; and Department of Nephrology, Dialysis and Transplantation, San Bortolo Hospital, Vicenza, Italy

Introduction

Acute kidney injury (AKI) is a multifactorial disease. It commonly complicates high-risk surgeries and appears as a consequence of systemic illness or injury [1]. More than 50% of intensive care unit (ICU) patients develop AKI (defined by Kidney Disease: Improving Global Outcomes [KDIGO] criteria), with ≥30% of these patients reaching the more severe KDIGO stages (stage 2 and 3) [2, 3]. Multiple studies have identified AKI as an important risk factor for high morbidity and mortality. Furthermore, it significantly increases the need for renal replacement therapy (RRT), hospital costs, and leads to end-stage renal disease (ESRD) or chronic kidney disease (CKD) [4, 5]. Despite increasing attention in recent years, little improvement in outcomes of AKI has occurred. There are two major challenges, the difficulty to detect AKI early and the poor understanding of its pathogenesis, have hampered the progress in AKI research and clinical management [1]. Current definitions of AKI including the risk, injury, failure, loss of function, ESRD, the Acute Kidney Injury

Network, and the KDIGO criteria all rely on changes in either the levels of serum creatinine (sCr) and/or urinary output [6–9]. sCr and oliguria are neither sensitive nor specific. Because both of them are markers of kidney function not of kidney injury or stress, and are easily influenced by many factors (including sex, muscle mass, medications or volume status), so using them may delay the diagnosis of AKI [1, 10]. Over the past decade, there have been numerous studies dedicated to discovering novel makers for an early detection of AKI in order to reverse the adverse outcomes of AKI. These biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18), liver-type fatty acid binding protein (L-FABP), kidney injury molecule-1 (KIM-1), tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor-binding protein 7 (IGFBP7) [11–14]. Among all these markers, [TIMP-2] · [IGFBP7] shows the best accuracy and stability, even in patients with chronic conditions such as diabetes mellitus, congestive heart failure and CKD [15]. In 2014, the Food and Drug Administration (FDA) approved the test "NephroCheck®" (Astute Medical, San Diego, CA, USA) ([TIMP-2] · [IGFBP7], united in $[ng/mL]^2/1000$) to be used in ICU patients to predict the risk of developing moderate to severe AKI within the prior 24 h [16]. Since then, more and more studies focused on the evaluation of the clinical application of NephroCheck®. In this review, we summarize the current research status of cell cycle arrest biomarkers (TIMP-2 and IGFBP7), and discuss the advantages and limitations of using these biomarkers.

Biological characteristics

TIMP-2 has a molecular weight of approximately 24 kDa and IGFBP7 has a molecular mass of 29 kDa [17]. Both of them are expressed and secreted by renal tubular cells, and involved in G1 cell cycle arrest during the early phases of cellular stress or injury caused by various insults (e.g. sepsis, ischemia, oxidative stress and toxins) [18].

In addition to the quiescent state (G0), the cell cycle includes four tightly controlled phases: G1, S (DNA synthesis), G2, and M (mitosis) [19]. Each phase of the cell cycle has a specific function for appropriate cell proliferation. Cells must enter and exit each phase of the cell cycle on schedule in order to divide and repair. This process is controlled by cyclins, cyclin-dependent kinases (CDK), and cyclin-dependent kinases inhibitors. If the cells stay in a phase too long or exit a phase too soon, the normal division and repair process can become maladaptive [20]. For instance, if the cells remain arrested in G1 or G2 phase instead of re-initiating the cell cycle, a senescent, hypertrophic and fibrotic cell phenotype will present. Conversely, exiting from the cell cycle in late G1 phase may lead to cell apoptosis [21].

When exposed to cellular stress or injury, renal tubular cells may produce and release TIMP-2 and IGFBP7. TIMP-2 stimulates p27 expression and IGFBP7 directly increases the expression of p53 and p21. Then these p proteins block the effect of cyclin-dependent protein kinase complexes (CyclD-CDK4 and CyclE-CDK2) on cell cycle promotion, resulting in transient G1 cell cycle arrest, thereby providing cells an opportunity to repair DNA damage and regain function. This process happens during early cellular stress and may help cells maintain energy balance, prevent further DNA damage and division [22, 23]. But sustained cell cycle arrest will result in a senescent cell phenotype and lead to fibrosis. So cell cycle arrest is not only associated with increased risk for AKI but may also serve as a mechanistic link between AKI and CKD [19, 24] (Figure 1).

Clinical research

Before clinical application of NephroCheck®, there have been three main studies for detecting and validating the ability of [TIMP-2] · [IGFBP7] to pre-diagnose AKI. These studies are summarized below and in Table 1.

The Sapphire study was a multicenter observational study in heterogeneous critically-ill patients, which had two phases: discovery phase and validation phase. The primary endpoint was moderate-severe AKI (KDIGO stage 2–3) within 12 h of sample collection. The purpose of the discovery phase study was to identify novel potential biomarkers for AKI. In this phase, 522 adult ICU patients were enrolled and 340 biomarkers in the urine and blood were tested (including NGAL, KIM-1, IL-18, L-FABP). As shown by the results, TIMP-2 and IGFBP7 had the best performance, with an area under the receiver operating characteristic curve (AUC) of 0.80 for [TIMP-2] · [IGFBP7] (0.79 and 0.76, respectively), which was significantly superior to all previously described markers of AKI ($p < 0.002$) [23]. Subsequently, the outcome was validated in the validation phase study which included a heterogeneous sample of 728 critically-ill patients. The combined urine biomarker product of [TIMP-2] · [IGFBP7] was proved to be stable across clinical syndromes and significantly improved risk stratification [1].

The Opal study was a derivation and validation study to confirm the accuracy and clinical utility of two different cutoff values of [TIMP-2] · [IGFBP7] in 154 adult critically-ill patients from six sites in the US. In this study, the researchers set the cutoff of 0.3 $(ng/mL)^2/1000$ for

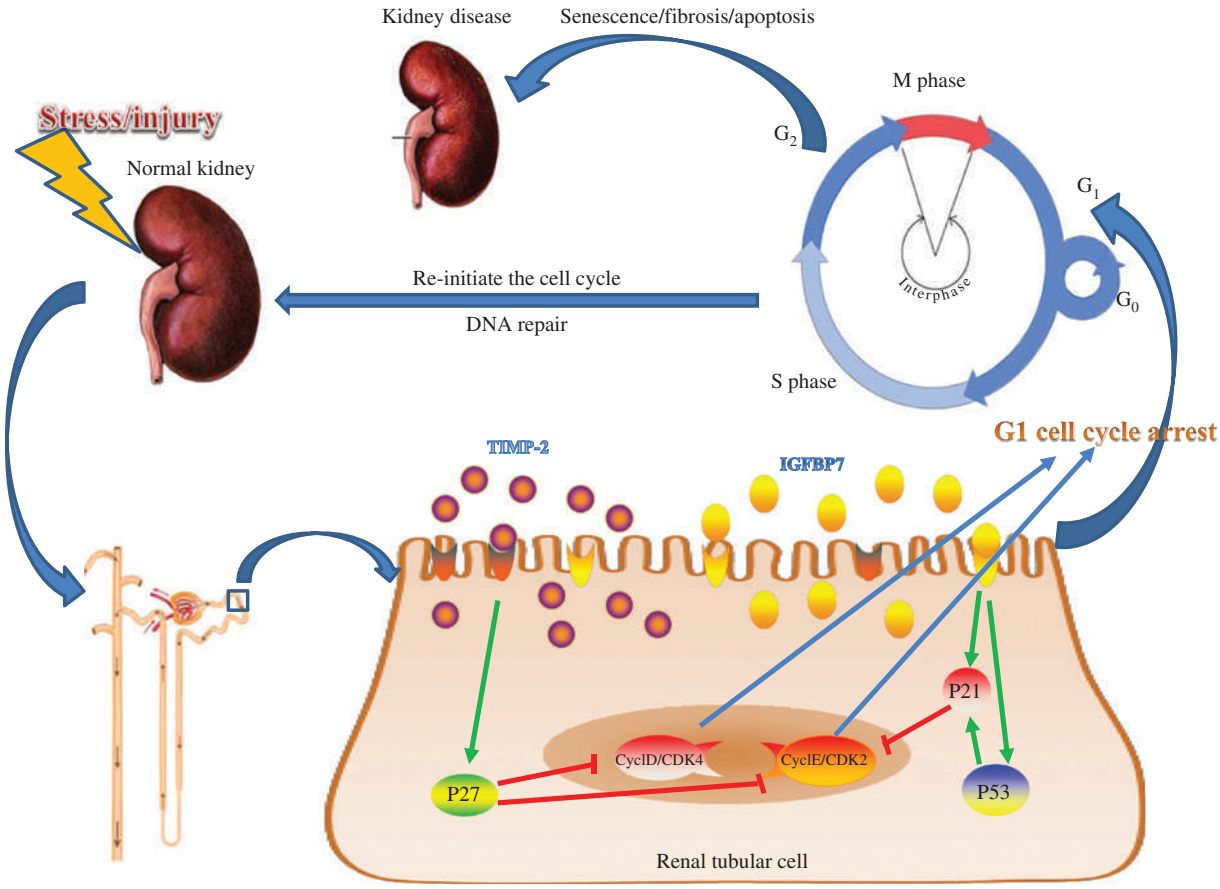


Figure 1: Mechanism of TIMP-2 and IGFBP7 in AKI.

Table 1: Derivation and validation studies of TIMP-2 and IGFBP7 for predicting AKI before clinical application.

Study name, number	Goal	Study population	End point	Main results
Sapphire study				
Discovery phase (522)	Identify novel biomarkers for detecting AKI	ICU patients >21 years old, with at least one risk factor for AKI	Moderate or severe AKI (KDIGO stage 2–3)	340 potential biomarkers were tested, TIMP-7 and IGFBP7 were the best performing markers (AUC: 0.79 and 0.76, respectively)
Validation phase (728)	Validation the performance of TIMP-2 and IGFBP7 for detecting AKI			14% reached primary end point; risk of AKI was significantly elevated with [TIMP-2] · [IGFBP7] >0.3
Opal study (154)	Derivated and validate two different cutoff values of [TIMP-2] · [IGFBP7]			18% reached primary end point; AUC was 0.79. For 0.3 cutoff, sensitivity was 89%, and NPV was 97%. For 2.0 cutoff, specificity was 95% and PPV was 49%.
Topaz study (420)	Validate the performance of [TIMP-2] · [IGFBP7] with clinical adjudication		Moderate or severe AKI (judged by three nephrologist who blinded to the results)	17.4% reached primary end point; AUC was 0.82. For 0.3 cutoff, sensitivity was 92% and specificity was 46%; For 2.0 cutoff, sensitivity was 46% and specificity was 95%. [TIMP-2] · [IGFBP7] remained significant when combined with clinical model.

TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7; AKI, acute kidney injury; ICU, intensive care unit; AUC, area under curve; NPV, negative predictive value; PPV, positive predictive value.

high sensitivity/high negative predictive value (NPV) and 2.0 $(ng/mL)^2/1000$ for high specificity/high positive predictive value (PPV). The results of the Opal study replicated those of the Sapphire study where the sensitivity at the 0.3 cutoff was 89%, and NPV was 97%. For 2.0 cutoff, specificity was 95% and PPV was 49% [25].

The Topaz study enrolled 420 heterogeneous critically-ill patients in order to prospectively validate the lower (0.3) cutoff value for risk assessment of AKI. In this study, the endpoint was determined independently by clinical adjudication by three nephrologists who were blinded to the results of the test. [TIMP-2] · [IGFBP7] significantly improved risk assessment, with a seven-fold increase in risk for patients with [TIMP-2] · [IGFBP7] value >0.3 compared with those ≤0.3 [26].

Thus, urinary [TIMP-2] · [IGFBP7] has now been shown to provide early detection and risk stratification for imminent AKI in over 1800 heterogeneous critically-ill patients. Since the publication of the Sapphire, Opal, and Topaz studies, NephroCheck® was approved by the FDA in 2014 to help determine whether critically-ill patients are at risk of development of moderate to severe AKI, both in the United States and Europe. From then on, more and more studies have been dedicated to clarifying the validity of [TIMP-2] · [IGFBP7] for predicting AKI in ICU patients. Some of the results are positive, such as those reported by Di Leo et al. demonstrating that [TIMP-2] · [IGFBP7] at ICU admission has a good performance in predicting AKI [27]. In contrast, some results are negative, for example, Bell et al. found that [TIMP-2] · [IGFBP7] did not predict AKI within 12–48 h and were significantly affected by comorbidities (e.g. diabetes) [28]. Additionally, some studies aimed to identify the utility of [TIMP-2] · [IGFBP7] in multiple clinical settings.

Research of [TIMP-2] · [IGFBP7] in AKI associated with different etiologies

AKI is a multi-etiological disease, many studies have tried to clarify the practicality of urinary [TIMP-2] · [IGFBP7] in AKI of different etiologies. The major and recent studies in this regard are listed in Table 2.

Cardiac surgery

Patients undergoing cardiac surgery are at high risk for AKI. A recent meta-analysis estimated the global incidence of AKI following cardiac surgery in adults to be approximately 22% [49]. Most current clinical studies on [TIMP-2] · [IGFBP7] focus on cardiac surgery-associated AKI. In Meersch et al.'s study, [TIMP-2] · [IGFBP7] had an AUC of 0.84 for predicting AKI stage 2–3 after cardiac surgery, whereas, sensitivity and specificity were 0.92 and 0.81, respectively, for a cutoff value of 0.50. Additionally, they demonstrated that decline in urinary [TIMP-2] · [IGFBP7] values was an accurate predictor for renal recovery [29]. At the same time, previously published cutoff points of 0.3 and 2.0 could not be confirmed in Wetz et al.'s study cohort. In contrast, they found a cutoff point of 1.1 with an AUC of 0.71 (sensitivity was 0.47, specificity was 0.96) [30]. At the same time, Pilarczyk et al. found an AUC of 0.861 (sensitivity 0.83, specificity 0.67) for predicting AKI stage 2–3 4 h after surgery at cut-off 0.15 [31]. Dusse et al. found an AUC of 0.97 (sensitivity 1.00, specificity 0.90) for predicting AKI stage 2–3 on day 1 after transcatheter aortic valve implantation surgery at cut-off 1.03 [32]. Wang et al. validated the performance of [TIMP-2] · [IGFBP7] in a Chinese population of cardiac surgery patients. They concluded that [TIMP-2] · [IGFBP7] 4 h after postoperative ICU admission identifies patients at risk of developing AKI, the AUC was 0.83 [33]. Oezkur et al. investigated the association of [TIMP-2] · [IGFBP7] at various time points with the incidence of AKI in a prospective study enrolling 150 cardiac surgery patients. They demonstrated that measurement of [TIMP-2] · [IGFBP7] at ICU admission directly after surgery is a strong and accurate predictor of AKI within 48 h after surgery [34]. Levante et al. [35] and Mayer et al. [36] confirmed the ability of [TIMP-2] · [IGFBP7] for predicting AKI in their studies. In contrast, a recent study by Zaouter et al. failed to demonstrate the ability of [TIMP-2] · [IGFBP7] for predicting cardiac surgery-associated AKI occurring in the first post-operative week within the first 24 postoperative hours [37]. Therefore, although many studies have investigated the ability of [TIMP-2] · [IGFBP7] to predict AKI after cardiac surgery, the results (cutoff, test time, AUC) are inconsistent and further large-scale studies are needed.

Major surgery

AKI also commonly complicates high-risk non-cardiac surgery which has received much less attention than cardiac surgery [50]. As demonstrated in Gocze et al. and Gunnerson et al.'s study, the [TIMP-2] · [IGFBP7] was a strong predictor of AKI and significantly improved the risk assessment. The AUC for the risk of AKI was 0.85 and 0.84 in each study. In Gocze et al.'s study, they also conducted

Table 2: Researches of [TIMP-2]·[IGFBP7] in AKI associated with different etiologies.

The cause of AKI	Study	Patient population	AKI diagnostic criteria	AKI threshold	No. of patients enrolled/no. of patients developed AKI	[TIMP-2]·[IGFBP7] detection time	AUC	Cut off	Sensitivity	Specificity
Cardiac surgery	Meersch et al. [29] (2014; Germany)	Patients undergoing cardiac surgery with CPB	KDIGO	AKI stage ≥1 within 72 h after surgery	50/26	4 h after CPB	0.81 0.84	0.3 0.5	0.80 0.92	0.83 0.81
	Wetz et al. [30] (2015; Germany)	Patients (≥18 years) undergoing CABG surgery with CPB	KDIGO	AKI stage ≥1 within 2 postoperative days	42/16	1 day after surgery	0.71	0.3 2.0 1.1	0.53 0.33 0.47	0.54 1.00 0.96
	Pilarczyk et al. [31] (2015; Germany)	Patients undergoing on-pump CABG	KDIGO	AKI stage ≥2 within 48 h after surgery	60/19	4 h after CABG	0.86	0.15	0.83	0.67
	Dusse et al. [32] (2016; Germany)	Patients undergoing TAVI	KDIGO	AKI stage ≥2 within 48 h after surgery	40/15	At 1 postoperative day	0.97	1.03	1.00	0.90
	Wang et al. [33] (2017; China)	Patients (≥18 years) undergoing cardiac surgery	KDIGO	AKI stage ≥1 within 7 days after surgery	57/20	4 h after postoperative ICU admission	0.80	0.3 2.0	0.75 0.20	0.70 1.00
	Oezkur et al. [34] (2017; Germany)	Patients undergoing cardiac surgery with CPB	KDIGO	AKI stage ≥1 within 48 h after surgery	150/35	At postoperative ICU admission	0.81	0.3	0.60	0.88
	Levante et al. [35] (2017; Italy)	Patients (≥18 years) undergoing cardiac surgery	KDIGO	AKI within 10 days after surgery	442/?	12 h after surgery	0.92	0.3	0.84	0.88
	Mayer et al. [36] (2017; Switzerland)	Patients undergoing cardiac surgery with CPB	KDIGO	AKI stage ≥1 after surgery	110/9	1 h after starting CPB	NR	0.4	0.78	0.64
	Zaouter et al. [37] (2018; France)	Patients undergoing on-pump heart surgery	KDIGO	AKI stage ≥1 within 7 days after surgery	50/37	12 h after surgery	0.69	0.3	0.65	0.62
Major surgery	Gocze et al. [38] (2015; Germany)	Surgical patients (≥18 years) at high risk for AKI	KDIGO	AKI stage ≥1 within 48 h	107/45	At enrollment	0.85	0.3	0.87	0.73
	Gunnerson et al. [39] (2015; US and Europe)	Surgical patients (≥21 years) at high risk for AKI	KDIGO	AKI stage ≥2 within 12 h	375/35	At ICU admission	0.84	0.3 2.0	0.89 0.40	0.49 0.94
Kidney transplantation (KT)	Pianta et al. [40] (2015; Australia)	Patients underwent KT	Development of DGF	Requirement for dialysis within 7 days	56/22	4 h after kidney reperfusion	0.76	0.3	0.72	0.81
	Yang et al. [41] (2017; Korea)	Patients underwent KT	Development of DGF	Requirement for dialysis within 7 days	74/23	Immediately after the operation	0.87	1.39	0.86	0.71
Decompensated heart failure	Schanz et al. [42] (2017; Germany)	Patients admitted to ICU with ADHF enrolled in ED	KDIGO	AKI stage ≥2 within 24 h	40/11	Within 24 h of enrollment	0.84	0.3 2.0	0.86 0.43	0.73 0.95
Cardiac arrest	Beitland et al. [43] (2016; Norway)	Patients (≥18 years) with comatose OHCA	KDIGO	AKI stage ≥1 within 72 h	196/88	At admission	0.77	0.36	NR	NR
	Adler et al. [44] (2018; Germany)	Patients with non-traumatic OHCA	KDIGO	AKI stage ≥1 within 72 h	48/31	3 h after OHCA	0.97	0.24	0.97	0.94
Sepsis	Honore et al. [45] (2016; Europe and North America)	Patients with sepsis	KDIGO	AKI stage ≥2 within 12 h	232/40	At ICU admission	0.84	0.3 1.0 2.0	0.95 0.78 0.60	0.38 0.75 0.89
	Cuartero et al. [46] (2017; Spain)	Patients (≥18 years) admitted to ICU	AKIN	AKI within 48 h	98/49	Within 12 h of ICU admission	0.80	0.4 0.8	0.74 0.72	0.71 0.78

Table 2 (continued)

The cause of AKI	Study	Patient population	AKI diagnostic criteria	AKI threshold	No. of patients enrolled/no. of patients developed AKI	[TIMP-2] · [IGFBP7] detection time	AUC	Cut off	Sensitivity	Specificity
Toxic renal disease	Schanz et al. [47] (2017; Germany)	Patients with malignant neoplastic disease, therapy with cisplatin or carboplatin	KDIGO	AKI stage ≥1 within 72 h after the administration of chemotherapy	58/4	Within 12 h after chemotherapy administration	0.92	0.3	0.50	0.87
	Toprak et al. [48] (2017; Turkey)	Patients with lung cancer with cisplatin containing chemotherapy	AKIN	AKI within 48 h	45/13	24 h after cisplatin administration	0.46	NR	NR	NR

ADHF, acute decompensated heart failure; AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; AUC, area under the receiver operating characteristic curve; CABG, coronary artery bypass surgery; CPB, cardiopulmonary bypass; DGF, delayed graft function; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; KT, kidney transplantation; NR, not report; OHCA, out-of-hospital cardiac arrest; TAVI, transcatheter aortic valve implantation; TIMP-2, tissue inhibitor of metalloproteinases-2; IGFBP7, insulin-like growth factor-binding protein 7.

an AUC for early use of RRT (0.83) and for 28-day mortality (0.77) [38, 39]. So using [TIMP-2] · [IGFBP7] may not only predict AKI, but can also guide the early initiation of kidney protection treatment and predict AKI prognosis.

Kidney transplantation

Pianta et al. assessed the utility of [TIMP-2] · [IGFBP7] and five inflammatory markers to predict delayed graft function (DGF) following deceased-donor kidney transplantation in 56 recipients. Only TIMP-2 and vascular endothelial growth factor-A, not [TIMP-2] · [IGFBP7], significantly enhanced the DGF prediction at 4 and 12 h [40]. In contrast, Yang et al. indicated that [TIMP-2] · [IGFBP7] test immediately after transplantation could be an early, predictive biomarker of DGF in kidney transplantation, with an AUC of 0.867 (sensitivity 0.86, specificity 0.71) for a cutoff value of 1.39 [41].

Decompensated heart failure

Acute decompensated heart failure (ADHF) is another disease associated with a high risk of AKI, but the research in this area is limited. In Schanz et al.'s study, they examined the predictive ability of urinary [TIMP-2] · [IGFBP7] for development of AKI stage 2 or 3 within 24 h of sample collection. Of the ADHF patients 27.5% developed AKI stage 2–3 within 7 days. Urinary [TIMP-2] · [IGFBP7] discriminated AKI stage 2–3 over the first day with an AUC of 0.84, sensitivity was 86% at the 0.3 cutoff and specificity was 95% at the 2.0 cutoff. They concluded that in patients with ADHF, urinary [TIMP-2] · [IGFBP7] is associated with moderate to severe AKI and related to increased mortality [42].

Cardiac arrest

Patients after cardiac arrest are predisposed to development of multiple organ failure, especially AKI, due to ischemia-reperfusion injury. [TIMP-2] · [IGFBP7] levels only predicted AKI in urine samples collected at admission, but, was not significantly associated with the development of AKI at day 3 as confirmed by Beitland et al.'s study [43]. In a recent research study, Adler et al. found that urinary [TIMP-2] · [IGFBP7] reliably predicts AKI in high-risk patients only 3 h after determination of cardiac arrest with a cut-off at 0.24 [44]. Research in this area is still very limited. Further larger-sample studies are needed

to confirm which biomarker has better clinical utility of predicting AKI.

Sepsis

Sepsis is a major cause for AKI. In fact, almost half of AKI is caused by sepsis [51, 52]. The [TIMP-2] · [IGFBP7] test provides accurate prediction of AKI in septic patients and the test performance is not affected by non-renal organ dysfunction, as was confirmed in Honore et al.'s study [45]. Cuartero et al. presented a prospective, observational study including 98 ICU patients to examine the role of [TIMP-2] · [IGFBP7] in septic AKI and non-septic AKI. The AUC to predict AKI was 0.798 (sensitivity 73.5%, specificity 71.4%). [TIMP-2] · [IGFBP7] was found to be an early predictor of AKI in ICU patients regardless of sepsis. Moreover, [TIMP-2] · [IGFBP7] values <0.8 $(ng/mL)^2/1000$ ruled out the need for RRT [46]. This study showed that [TIMP-2] · [IGFBP7] is associated with AKI, but is not specific for sepsis.

Toxic renal disease

Platinum-based chemotherapy (PBC) is broadly used potent antineoplastic treatments, with potential nephrotoxicity, especially of cisplatin. Schanz et al. conducted a clinical observational study enrolling 58 patients with malignant neoplastic disease, four (12.5%) patients developed AKI within 72 h. In their study, urinary [TIMP-2] · [IGFBP7] values after the administration of PBC were significantly higher in patients with AKI than those without AKI. The AUC was 0.92. At the cutoff of 0.3 for [TIMP-2] · [IGFBP7], sensitivity was 50%, specificity was 87%, NPV was 95% and PPV was 25% for the prediction of AKI within 72 h. So they concluded that urinary [TIMP-2] · [IGFBP7] measured after PBC may be a useful tool for early identification of patients at risk of developing platinum-induced AKI [47]. In contrast, in Toprak et al.'s study, those findings were not replicated [48]. Overall, these two studies had small sample size. Larger studies are required to determine whether [TIMP-2] · [IGFBP7] can predict cisplatin-related AKI.

Future directions

To date, the published literature about [TIMP-2] · [IGFBP7] mainly focuses on the application of [TIMP-2] · [IGFBP7] in adult ICU patients who develop ischemic- or nephrotoxic-AKI as already described. Pajenda et al. tested [TIMP-2] · [IGFBP7] in 69 patients with different settings of AKI. They indicated that in patients with ischemic reperfusion and toxic injury, the values of [TIMP-2] · [IGFBP7] rise and decline rapidly, even before polyuria becomes evident. Furthermore, they confirmed that when [TIMP-2] · [IGFBP7] value remains below 8, the concomitant rise in sCr and the stage of AKI appear to be reversible. Conversely, [TIMP-2] · [IGFBP7] value of more than 18 that remained elevated for a long time indicated that the kidney function is unrecoverable and patients would require RRT permanently [53]. Whether [TIMP-2] · [IGFBP7] use can be expanded in other contexts or patient populations, such as pediatric patients has not been confirmed.

The performance data of [TIMP-2] · [IGFBP7] in different patient populations outside the ICU or perioperative setting is still lacking [13]. Some studies showed that [TIMP-2] · [IGFBP7] provides independent prediction of AKI in emergency department patients as well [54, 55]. As far as its use in the pediatric population, one study looking at [TIMP-2] · [IGFBP7] level following cardiac surgery implied that [TIMP-2] · [IGFBP7] alone is not suitable for predicting AKI in this patient population [56]. Another study demonstrated that [TIMP-2] · [IGFBP7] can be used in infants to predict AKI following cardiopulmonary bypass [57]. Meanwhile, more studies are needed to confirm the clinical utility of [TIMP-2] · [IGFBP7] in other causes of AKI (e.g. acute interstitial AKI, post-renal AKI).

Recognizing the major risks associated with AKI and in an attempt to potentially reverse its adverse outcomes, the FDA has taken an important step to provide us with a new tool as an early alert of which patients are at imminent risk [58]. However, because AKI is often multifactorial, it seems unlikely that a single AKI biomarker would achieve troponin-like diagnostic accuracy. So like all diagnostic tests, NephroCheck® is not a standalone test, it needs to be combined with clinical judgment (such as urine sediment score) in order to detect AKI with higher sensitivity and specificity [59]. Therefore, in future studies, how to combine NephroCheck® test with other clinical examinations or symptoms to improve diagnostic accuracy is an important research direction.

TIMP-2 and IGFBP7 do not appear to persist in the urine for long after AKI, meanwhile, the combination of them is more sensitive to transient AKI with a higher delta NephroCheck® score comparing to persistent AKI [60]. Furthermore, the concentration of [TIMP-2] · [IGFBP7] does not depend on the expression of *TIMP-2* and the *IGFBP7* gene in cells of the urinary sediment. In addition, there is no correlation between [TIMP-2] · [IGFBP7] with sCr, BUN or eGFR [61]. Therefore, NephroCheck® may be normal in patients

who have already manifested AKI by functional criteria (e.g. sCr). AKI complicating critical illness is highly heterogeneous in severity, etiology and timing, so defining the appropriate timing and frequency of biomarker measurement and interpreting these results in individual patients is extremely difficult [62]. However, it is very meaningful to verify the best time and frequency of NephroCheck® test, for example, it can save unnecessary testing costs.

Some researchers suggest that [TIMP-2] · [IGFBP7] for the prediction of AKI might be most applicable in patients at high risk of AKI, and less precise in those at lower risk [63]. Among patients with AKI risk, applying high-sensitivity threshold could focus patient care on strategies of intensified monitoring prior to any increase in sCr. Furthermore, combining AKI diagnostic criteria (such as KDIGO criteria) with NephroCheck® test results may enable us to predict the development trend of AKI, recovery or progress to the next phase of AKI. In this way, NephroCheck® could be utilized and integrated with additional clinical information to help inform more complex and invasive management decisions, such as prediction of the need for RRT, and deciding when to start or stop RRT [64]. Meanwhile, the cost benefit of [TIMP-2] · [IGFBP7] test is unknown. We need more clinical trials and data to support the hypothesis that early recognition of kidney injury with [TIMP-2] · [IGFBP7] will prevent the progression of AKI or be associated with a cost benefit to the patient or institution, avoiding unnecessary and expensive diagnostic and therapeutic evaluations.

Furthermore, measurement of [TIMP-2] · [IGFBP7] not only provides information for predicting and diagnosing AKI, but also has the potential to help to identify patients who are at the highest risk of developing adverse outcomes [65–67]. Further studies to evaluate the predictive value of [TIMP-2] · [IGFBP7] for ICU stay, mortality and progression to ESRD, are needed. Moreover, the current studies looking into the mechanism by which the test works is still in the hypothesis phase, additional studies using conditional knockouts and pharmacologic inhibitors of TIMP-2 and IGFBP7 are needed to better define its mechanistic role in renal injury [68]. As a result, cell cycle regulation may become a potential new target for the prevention and treatment of AKI. We may even be able to prevent CKD progression by regulating cell cycle arrest [69].

Conclusions

As a novel biomarker for predicting AKI, [TIMP-2] · [IGFBP7] has already proved its validity and accuracy in multiple studies in many fields and has been applied by the FDA for clinical application. Further studies regarding the application value of [TIMP-2] · [IGFBP7] in different clinical contexts, different patient populations, different disease spectrum, are needed. It is important to translate this advancement in AKI biomarkers to meaningful improvement in clinical care and treatment strategy, in order to achieve better outcomes.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.
Research funding: None declared.
Employment or leadership: None declared.
Honorarium: None declared.
Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

References

1. Kellum JA, Chawla LS. Cell-cycle arrest and acute kidney injury: the light and the dark sides. Nephrol Dial Transplant 2016;31:16–22.
2. Schetz M, Schneider A. Focus on acute kidney injury. Intensive Care Med 2017;43:1421–3.
3. Negi S, Koreeda D, Kobayashi S, Yano T, Tatsuta K, Mina T, et al. Acute kidney injury: epidemiology, outcomes, complications, and therapeutic strategies. Semin Dial 2018 May 8. doi:10.1111/sdi.12705. [Epub ahead of print].
4. Ronco C, Rizo-Topete L, Serrano-Soto M, Kashani K. Pro: prevention of acute kidney injury: time for teamwork and new biomarkers. Nephrol Dial Transplant 2017;32:408–13.
5. Maxwell RA, Bell CM. Acute kidney injury in the critically ill. Surg Clin North Am 2017;97:1399–418.
6. Makris K, Spanou L. Acute kidney injury: definition, pathophysiology and clinical phenotypes. Clin Biochem Rev 2016;37:85–98.
7. Bellomo R, Ronco C, Kellum JA, Mehta RL, Acute Dialysis Quality Initiative workgroup. Acute renal failure – definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–12.
8. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.
9. Acute Kidney Injury Work Group KDIGO. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group KDIGO clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1–138.
10. Prowle JR, Liu YL, Licari E, Bagshaw SM, Egi M, Haase M, et al. Oliguria as predictive biomarker of acute kidney injury in critically ill patients. Crit Care 2011;15:R172.

11. Murray P, Mehta R, Shaw A, Ronco C, Endre Z, Kellum J, et al. Current use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th acute dialysis quality initiative consensus conference. Kidney Int 2014;85:513–21.
12. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). Best Pract Res Clin Anaesthesiol 2017;31:331–44.
13. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. Clin Chem Lab Med 2017;55:1074–89.
14. Pozzoli S, Simonini M, Manunta P. Predicting acute kidney injury: current status and future challenges. J Nephrol 2018;31:209–23.
15. Heung M, Ortega LM, Chawla LS, Wunderink RG, Self WH, Koyner JL, et al. Common chronic conditions do not affect performance of cell cycle arrest biomarkers for risk stratification of acute kidney injury. Nephrol Dial Transplant 2016;31:1633–40.
16. Vijayan A, Faubel S, Askenazi DJ, Cerda J, Fissell WH, Heung M, et al. Clinical use of the urine biomarker [TIMP-2] × [IGFBP7] for acute kidney injury risk assessment. Am J Kidney Dis 2016;68:19–28.
17. Emlet DR, Pastor-Soler N, Marciszyn A, Wen X, Gomez H, Humphries WH 4th, et al. Insulin-like growth factor binding protein 7 and tissue inhibitor of metalloproteinases-2: differential expression and secretion in human kidney tubule cells. Am J Physiol Renal Physiol 2017;312:F284–96.
18. Ortega LM, Heung M. The use of cell cycle arrest biomarkers in the early detection of acute kidney injury. Is this the new renal troponin? Nefrologia 2018;38:361–7.
19. Andrade L, Rodrigues CE, Gomes SA, Noronha IL. Acute kidney injury as a condition of renal senescence. Cell Transplant 2018;27:739–53.
20. Shankland SJ. Cell cycle regulatory proteins in glomerular disease. Kidney Int 1999;56:1208–15.
21. Ferenbach DA, Bonventre JV. Mechanisms of maladaptive repair after AKI leading to accelerated kidney ageing and CKD. Nat Rev Nephrol 2015;11:264–76.
22. Wang W, Saad A, Herrmann SM, Eirin Massat A, McKusick MA, Misra S, et al. Changes in inflammatory biomarkers after renal revascularization in atherosclerotic renal artery stenosis. Nephrol Dial Transplant 2016;31:1437–43.
23. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013;17:R25.
24. Yang L, Besschetnova TY, Brooks CR, Shah JV, Bonventre JV. Epithelial cell cycle arrest in G2/M mediates kidney fibrosis after injury. Nat Med 2010;16:535–43.
25. Hoste EA, McCullough PA, Kashani K, Chawla LS, Joannidis M, Shaw AD, et al. Derivation and validation of cutoffs for clinical use of cell cycle arrest biomarkers. Nephrol Dial Transplant 2014;29:2054–61.
26. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, Demuth GE, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med 2014;189:932–9.
27. Di Leo L, Nalesso F, Garzotto F, Xie Y, Yang B, Virzì GM, et al. Predicting acute kidney injury in intensive care unit patients: the role of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein-7 biomarkers. Blood Purif 2018;45:270–7.
28. Bell M, Larsson A, Venge P, Bellomo R, Mårtensson J. Assessment of cell-cycle arrest biomarkers to predict early and delayed acute kidney injury. Dis Markers 2015;2015:158658.
29. Meersch M, Schmidt C, Van Aken H, Martens S, Rossaint J, Singbartl K, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. PLoS One 2014;9:e93460.
30. Wetz AJ, Richardt EM, Wand S, Kunze N, Schotola H, Quintel M, et al. Quantification of urinary TIMP-2 and IGFBP-7: an adequate diagnostic test to predict acute kidney injury after cardiac surgery? Crit Care 2015;19:3.
31. Pilarczyk K, Edayadiyil-Dudasova M, Wendt D, Demircioglu E, Benedik J, Dohle DS, et al. Urinary [TIMP-2]*[IGFBP7] for early prediction of acute kidney injury after coronary artery bypass surgery. Ann Intensive Care 2015;5:50.
32. Dusse F, Edayadiyil-Dudásova M, Thielmann M, Wendt D, Kahlert P, Demircioglu E, et al. Early prediction of acute kidney injury after transapical and transaortic aortic valve implantation with urinary G1 cell cycle arrest biomarkers. BMC Anesthesiol 2016;16:76.
33. Wang Y, Zou Z, Jin J, Teng J, Xu J, Shen B, et al. Urinary TIMP-2 and IGFBP7 for the prediction of acute kidney injury following cardiac surgery. BMC Nephrol 2017;18:177.
34. Oezkur M, Magyar A, Thomas P, Stork T, Schneider R, Bening C, et al. TIMP-2*IGFBP7 (Nephrocheck®) measurements at intensive care unit admission after cardiac surgery are predictive for acute kidney injury within 48 hours. Kidney Blood Press Res 2017;42:456–67.
35. Levante C, Ferrari F, Manenti C, Husain-Syed F, Scarpa M, Hinna Danesi T, et al. Routine adoption of TIMP2 and IGFBP7 biomarkers in cardiac surgery for early identification of acute kidney injury. Int J Artif Organs 2017;40:714–8.
36. Mayer T, Bolliger D, Scholz M, Reuthebuch O, Gregor M, Meier P, et al. Urine biomarkers of tubular renal cell damage for the prediction of acute kidney injury after cardiac surgery – a pilot study. J Cardiothorac Vasc Anesth 2017;31:2072–9.
37. Zaouter C, Potvin J, Bats ML, Beauvieux MC, Remy A, Ouattara A. A combined approach for the early recognition of acute kidney injury after adult cardiac surgery. Anaesth Crit Care Pain Med 2018;37:335–41.
38. Gocze I, Koch M, Renner P, Zeman F, Graf BM, Darlich M, et al. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. PLoS One 2015;10:e0120863.
39. Gunnerson KJ, Shaw AD, Chawla LS, Bihorac A, Al-Khafaji A, Kashani K, et al. TIMP2 · IGFBP7 biomarker panel accurately predicts acute kidney injury in high-risk surgical patients. J Trauma Acute Care Surg 2016;80:243–9.
40. Pianta TJ, Peake PW, Pickering JW, Kelleher M, Buckley NA, Endre ZH. Evaluation of biomarkers of cell cycle arrest and inflammation in prediction of dialysis or recovery after kidney transplantation. Transpl Int 2015;28:1392–404.
41. Yang J, Lim SY, Kim MG, Jung CW, Cho WY, Jo SK. Urinary tissue inhibitor of metalloproteinase and insulin-like growth factor-7 as early biomarkers of delayed graft function after kidney transplantation. Transplant Proc 2017;49:2050–4.
42. Schanz M, Shi J, Wasser C, Alscher MD, Kimmel M. Urinary [TIMP-2] × [IGFBP7] for risk prediction of acute kidney injury in decompensated heart failure. Clin Cardiol 2017;40:485–91.
43. Beitland S, Waldum-Grevbo BE, Nakstad ER, Berg JP, Trøseid AS, Brusletto BS, et al. Urine biomarkers give early prediction

of acute kidney injury and outcome after out-of-hospital cardiac arrest. Crit Care 2016;20:314.
44. Adler C, Heller T, Schregel F, Hagmann H, Hellmich M, Adler J, et al. TIMP-2/IGFBP7 predicts acute kidney injury in out-of-hospital cardiac arrest survivors. Crit Care 2018;22:126.
45. Honore PM, Nguyen HB, Gong M, Chawla LS, Bagshaw SM, Artigas A, et al. Urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 for risk stratification of acute kidney injury in patients with sepsis. Crit Care Med 2016;44:1851–60.
46. Cuartero M, Ballús J, Sabater J, Pérez X, Nin N, Ordonez-Llanos J, et al. Cell-cycle arrest biomarkers in urine to predict acute kidney injury in septic and non-septic critically ill patients. Ann Intensive Care 2017;7:92.
47. Schanz M, Hoferer A, Shi J, Alscher MD, Kinnel M. Urinary TIMP2 · IGFBP7 for the prediction of platinum-induced acute renal injury. Int J Nephrol Renovasc Dis 2017;10:175–81.
48. Toprak Z, Cebeci E, Helvaci SA, Toprak ID, Kutlu Y, Sakin A, et al. Cisplatin nephrotoxicity is not detected by urinary cell-cycle arrest biomarkers in lung cancer patients. Int Urol Nephrol 2017;49:1041–7.
49. Hu J, Chen R, Liu S, Yu X, Zou J, Ding X. Global incidence and outcomes of adult patients with acute kidney injury after cardiac surgery: a systematic review and meta-analysis. J Cardiothorac Vasc Anesth 2016;30:82–9.
50. Romagnoli S, Ricci Z, Ronco C. Perioperative acute kidney injury: prevention, early recognition, and supportive measures. Nephron2018 Jun 26. doi:10.1159/000490500. [Epub ahead of print].
51. Bagshaw SM, Uchino S, Bellomo R, Morimatsu H, Morgera S, Schetz M, et al. Septic acute kidney injury in critically ill patients: clinical characteristics and outcomes. Clin J Am Soc Nephrol 2007;2:431–9.
52. Bellomo R, Kellum JA, Ronco C, Wald R, Martensson J, Maiden M, et al. Acute kidney injury in sepsis. Intensive Care Med 2017;43:816–28.
53. Pajenda S, Ilhan-Mutlu A, Preusser M, Roka S, Drunl W, Wagner L. NephroCheck data compared to serum creatinine in various clinical settings. BMC Nephrol 2015;16:206.
54. Kimmel M, Shi J, Latus J, Wasser C, Kitterer D, Braun N, et al. Association of renal stress/damage and filtration biomarkers with subsequent AKI during hospitalization among patients presenting to the emergency department. Clin J Am Soc Nephrol 2016;11:938–46.
55. Kimmel M, Shi J, Wasser C, Biegger D, Alscher MD, Schanz MB. Urinary [TIMP-2] · [IGFBP7] – novel biomarkers to predict acute kidney injury. Am J Nephrol 2016;43:375–82.
56. Dong L, Ma Q, Bennett M, Devarajan P. Urinary biomarkers of cell cycle arrest are delayed predictors of acute kidney injury after pediatric cardiopulmonary bypass. Pediatr Nephrol 2017;32:2351–60.
57. Gist KM, Goldstein SL, Wrona J, Alten JA, Basu RK, Cooper DS, et al. Kinetics of the cell cycle arrest biomarkers (TIMP-2*IGFBP-7) for prediction of acute kidney injury in infants after cardiac surgery. Pediatr Nephrol 2017;32:1611–9.
58. Ronco C. Cell cycle arrest biomarkers: new weapons for a new battle. Blood Purif 2014;38:I–III.
59. US Food and Drug Administration. Evaluation of automatic class III designation for NephroCheck test system decision summary. Available at: https://www.accessdata.fda.gov/cdrh_docs/reciews/den130031.pdf.
60. Daubin D, Cristol JP, Dupuy AM, Kuster N, Besnard N, Platon L, et al. Urinary biomarkers IGFBP7 and TIMP-2 for the diagnostic assessment of transient and persistent acute kidney injury in critically ill patients. PLoS One 2017;12:e0169674.
61. Knafl D, Müller M, Pajenda S, Genc Z, Hecking M, Wagner L. The urine biomarker panel [IGFBP7]x[TIMP-2] (NephroCheck® parameter) does not correlate with IGFBP7 and TIMP-2 gene expression in urinary sediment. PLoS One 2017;12:e0188316.
62. Lameire N, Vanmassenhove J, Van Biesen W, Vanholder R. The cell cycle biomarkers: promising research, but do not oversell them. Clin Kidney J 2016;9:353–8.
63. Edwards JK. Biomarkers how precise is NephroCheck®? Nat Rev Nephrol 2015;11:127.
64. Clark WR, Neri M, Garzotto F, Ricci Z, Goldstein SL, Ding X, et al. The future of critical care: renal support in 2027. Crit Care 2017;21:92.
65. Jia HM, Huang LF, Zheng Y, Li WX. Prognostic value of cell cycle arrest biomarkers in patients at high risk for acute kidney injury: a systematic review and meta-analysis. Nephrology 2017;22:831–7.
66. Westhoff JH, Tönshoff B, Waldherr S, Pöschl J, Teufel U, Westhoff TH, et al. Urinary tissue inhibitor of metalloproteinase-2 (TIMP-2) · insulin-like growth factor-binding protein 7 (IGFBP7) predicts adverse outcome in pediatric acute kidney injury. PLoS One 2015;10:e0143628.
67. Koyner JL, Shaw AD, Chawla LS, Hoste EA, Bihorac A, Kashani K, et al. Tissue inhibitor metalloproteinase-2 (TIMP-2) IGF-binding protein-7 (IGFBP7) levels are associated with adverse long-term outcomes in patients with AKI. J Am Soc Nephrol 2015;26:1747–54.
68. Alge JL, Arthur JM. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. Clin J Am Soc Nephrol 2015;10:147–55.
69. Wang WG, Sun WX, Gao BS, Lian X, Zhou HL. Cell cycle arrest as a therapeutic target of acute kidney injury. Curr Protein Pept Sci 2017;18:1224–31.

Acute Kidney Injury, Mortality, Length of Stay, and Costs in Hospitalized Patients

Glenn M. Chertow,* Elisabeth Burdick,† Melissa Honour,† Joseph V. Bonventre,‡ and David W. Bates†

*Division of Nephrology, Departments of Medicine, Epidemiology, and Biostatistics, University of California San Francisco, San Francisco, California; †Division of General Internal Medicine and ‡Renal Division, Department of Medicine and Harvard-MIT Division of Health Sciences and Technology, Brigham and Women's Hospital, Harvard Medical School, Partners HealthCare System, Boston, Massachusetts

The marginal effects of acute kidney injury on in-hospital mortality, length of stay (LOS), and costs have not been well described. A consecutive sample of 19,982 adults who were admitted to an urban academic medical center, including 9210 who had two or more serum creatinine (SCr) determinations, was evaluated. The presence and degree of acute kidney injury were assessed using absolute and relative increases from baseline to peak SCr concentration during hospitalization. Large increases in SCr concentration were relatively rare (*e.g.*, ≥2.0 mg/dl in 105 [1%] patients), whereas more modest increases in SCr were common (*e.g.*, ≥0.5 mg/dl in 1237 [13%] patients). Modest changes in SCr were significantly associated with mortality, LOS, and costs, even after adjustment for age, gender, admission *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis, severity of illness (diagnosis-related group weight), and chronic kidney disease. For example, an increase in SCr ≥0.5 mg/dl was associated with a 6.5-fold (95% confidence interval 5.0 to 8.5) increase in the odds of death, a 3.5-d increase in LOS, and nearly $7500 in excess hospital costs. Acute kidney injury is associated with significantly increased mortality, LOS, and costs across a broad spectrum of conditions. Moreover, outcomes are related directly to the severity of acute kidney injury, whether characterized by nominal or percentage changes in serum creatinine.

J Am Soc Nephrol 16: 3365–3370, 2005. doi: 10.1681/ASN.2004090740

Acute kidney injury (AKI) has been reported in 5 to 7% of hospitalized patients on the basis of several single-center reports (1,2). Despite the perception that AKI is relatively common, there is no uniform definition for AKI, and relatively few data regarding its incidence in hospitalized patients are available. Moreover, the relative effects of AKI on mortality, hospital length of stay (LOS), and costs have not been well described. Most studies that have explored downstream effects of AKI have either considered AKI requiring dialysis or homogenous patient populations, such as those who were exposed to radiocontrast agents or undergoing cardiothoracic surgery.

In the context of a computer-based intervention in which data were collected on kidney function, severity of illness, drug prescription, and outcomes in hospitalized patients (3), we linked changes in serum creatinine (SCr) with in-hospital mortality, LOS, and costs. We hypothesized that relatively small changes in SCr would be common and associated with adverse outcomes, even after adjustment for severity of disease.

Received September 8, 2004. Accepted July 27, 2005.

Published online ahead of print. Publication date available at www.jasn.org.

Address correspondence to: Dr. Glenn M. Chertow, University of California San Francisco, Department of Medicine Research, UCSF Laurel Heights, Suite 430, 3333 California Street, San Francisco, CA 94118-1211. Phone: 415-476-2173; Fax: 415-476-9531; E-mail: chertowg@medicine.ucsf.edu

Materials and Methods

Study Setting

The study was conducted at Brigham and Women's Hospital, a 720-bed urban academic medical center in Boston, MA. Data were obtained for a study to examine the effects of a computer-order entry-based decision tool on drug prescribing for hospitalized patients with impaired kidney function (3). As part of the data library collected for evaluation of the appropriateness of drug prescription, serial SCr determinations were collected on a consecutive series of hospitalized patients on the medical, surgical (including subspecialty surgical services), neurology, and obstetrics and gynecology services between September 1997 and April 1998.

There were 19,982 admissions in which at least one SCr was obtained. For 9210 (46%) admissions, SCr was determined two or more times. Five (0.05%) admissions were excluded because vital status was unknown at discharge. The number of SCr determinations ranged from two to 92.

Description of Data

Routinely available demographic factors, specific drug prescriptions, Center for Medicare and Medicaid Services diagnosis-related group (DRG) weights (a proxy for disease severity [4]), LOS, hospital charges, itemized costs, and vital status at hospital discharge were also collected. For the purpose of these analyses, we additionally obtained primary *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for each hospitalization. We categorized the ICD-9-CM codes according to conventional methods. For risk adjustment, we grouped diagnoses into "diseases of the circulatory system," "diseases of the respiratory system," "diseases of the gastroin-

ISSN: 1046-6673/1611-3365

testinal system," "infectious diseases," "neoplasms," and all others, with the last group as the referent category. We considered people whose gender-stratified admission SCr was above the 90th percentile as "chronic kidney disease (CKD)," except when the admission ICD-9-CM code was 580, 584, or 788, potentially indicating community-acquired AKI. The CKD designation included men with SCr ≥ 1.6 mg/dl and women with SCr ≥ 1.4 mg/dl. We estimated baseline creatinine clearance using the Cockcroft-Gault equation, incorporating SCr, age, gender, and body weight (5).

To help determine the presence and severity of AKI, we calculated the difference between peak and baseline SCr concentrations. For individuals with only two SCr determinations, the second, when higher than the first, was considered the peak. We assumed that individuals with no further monitoring or change in SCr had not experienced AKI. For individuals with more than two SCr determinations, we considered the minimum of the first three as baseline and the maximum of the second through *n*th as peak. We considered nominal changes in SCr, percentage changes, percentage changes to a minimum peak, and other previously used algorithms that incorporated the exponential relation between SCr and GFR. Finally, we broadly classified individuals by a combination of ICD-9-CM diagnosis codes and prescribed medications as potentially associated with reduced renal perfusion ("prerenal") *versus* intrinsic renal injury.

Statistical Analyses

Continuous variables are described as mean ± SD or median with interquartile range and compared with *t* test or the Wilcoxon rank sum test, when appropriate. Categorical variables are described as proportions and compared with the χ^2 test. We used logistic regression to estimate the odds of death with AKI, adjusting for associations with age, gender, DRG weight, ICD-9-CM group, and CKD. Because death was relatively common among patients with large increases in SCr, risk ratios were estimated using the method of Zhang and Yu (6). Model discrimination was determined using the area under the receiver operating characteristic curve (7). Model fit was assessed with the Hosmer-Lemeshow goodness-of-fit test (8). We used linear regression analysis to evaluate the associations of AKI with hospital LOS and costs. We log-transformed LOS and costs to accommodate data that were expectedly right-skewed and used Mallow's Cp to assess model fit. Residual diagnostics indicated few outliers. We tested multiplicative interaction terms of AKI with other model covariates to evaluate for effect modification. To determine whether the risk associated with AKI differed by presumed cause (prerenal *versus* other), we used the Breslow-Day test for homogeneity of odds ratios (OR) and added an AKI × cause interaction term to multivariable models. Given that we were exploring multiple definitions of AKI and three outcome variables, we considered two-tailed $P < 0.01$ to be statistically significant. Statistical analyses were conducted using SAS 8.2 (SAS Institute, Cary, NC).

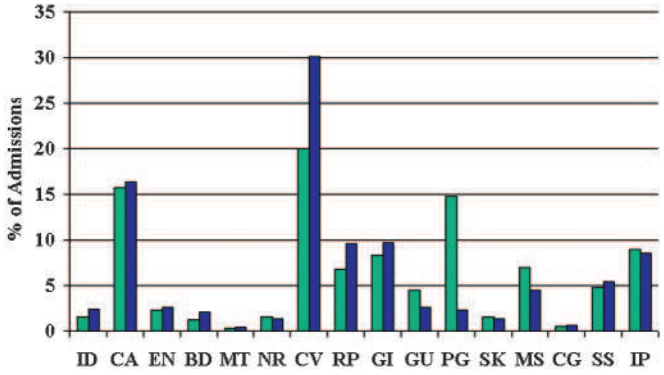


Figure 1. Distribution of admissions by *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) category. Teal bars refer to the sample of patients with one or more serum creatinine (SCr) determination(s); blue bars refer to the sample of patients with two or more SCr determinations. ID, infectious and parasitic disease; CA, neoplasms; EN, endocrine, nutritional, and metabolic diseases; BD, diseases of blood and blood forming organs; MT, mental disorders; NR, diseases of the nervous system; CV, diseases of the circulatory system; RP, diseases of the respiratory system; GI, diseases of the digestive system; GU, diseases of the genitourinary system; PG, complications of pregnancy, childbirth, and pureperium; SK, diseases of the skin and subcutaneous tissue; MS, diseases of the musculoskeletal system and connective tissue; CG, congenital anomalies; SS, symptoms, signs, and ill-defined conditions; IP, injury and poisoning.

Results

There were 19,982 admissions with one or more SCr determinations during the study period and 9205 with two or more (Table 1). Patients with two or more SCr determinations were more likely to be admitted with cardiovascular diseases, neoplasms, and respiratory diseases and less likely to be admitted for musculoskeletal diseases and issues related to pregnancy (Figure 1). No patients were admitted with a primary ICD-9-CM code of 585 (ESRD). As expected, disease severity was higher among patients with two or more SCr determinations, as were hospital LOS, total costs, and mortality. Of the 9205 patients with two or more SCr determinations, 7166 (78%), 5780 (63%), and 4682 (51%) had three, four, and five or more SCr

Table 1. Selected patient characteristics[a]

Factor	One Serum Creatinine Determination (n = 19,982)	Two or More Serum Creatinine Determinations (n = 9205)
Age (yr)	52.8 ± 15.4	58.8 ± 17.1
Gender (% female)	61%	51%
DRG weight	1.36 (0.86 to 3.17)	2.28 (1.19 to 3.88)
LOS (d)	3 (2–6)	5 (3–7)
Total costs (1998 $)	$5295 ($3141 to $10,748)	$7690 ($3919 to $13,952)
Hospital mortality (%)	2.3%	3.1%

[a]DRG weight, LOS, and costs expressed as median and interquartile range. DRG, diagnosis-related group; LOS, length of stay.

Table 2. Mortality associated with selected changes in SCr[a]

Criterion	Unadjusted OR (95% CI)	Age- and Gender-Adjusted OR (95% CI)	Multivariable OR (95% CI)[b]	Area under ROC Curve
↑ SCr ≥ 0.3 mg/dl	6.9 (5.2 to 9.0)	6.6 (5.0 to 8.7)	4.1 (3.1 to 5.5)	0.84
↑ SCr ≥ 0.5 mg/dl	11.1 (8.7 to 14.2)	10.6 (8.3 to 13.6)	6.5 (5.0 to 8.5)	0.86
↑ SCr ≥ 1.0 mg/dl	19.9 (15.1 to 26.1)	19.0 (14.4 to 25.0)	9.7 (7.1 to 13.2)	0.84
↑ SCr ≥ 2.0 mg/dl	36.4 (24.3 to 54.6)	37.7 (25.0 to 56.9)	16.4 (10.3 to 26.0)	0.83
↑ SCr by 25%	4.0 (3.0 to 5.2)	3.9 (3.0 to 5.2)	2.0 (1.2 to 3.9)	0.83
↑ SCr by 50%	5.9 (4.6 to 7.5)	5.8 (4.6 to 7.5)	4.4 (3.4 to 5.7)	0.84
↑ SCr by 100%	8.9 (6.9 to 11.4)	9.2 (7.1 to 11.8)	6.5 (4.9 to 8.6)	0.84
↑ SCr by 50% to a minimum peak of 2.0 mg/dl	16.9 (12.8 to 22.3)	15.9 (12.0 to 21.0)	7.9 (5.8 to 10.9)	0.84
↑ SCr ≥ 0.5 mg/dl with baseline SCr < 2.0 mg/dl or ↑ SCr ≥ 1.0 mg/dl with baseline SCr ≥ 2.0 and < 5.0 mg/dl	11.0 (8.6 to 14.0)	10.5 (8.2 to 13.4)	6.5 (5.0 to 8.5)	0.86

[a] n = 2892, 1236, 351, 105, 4060, 1967, 714, 352, and 1160 for respective acute kidney injury (AKI) criteria from denominator sample n = 9205. Results are relative to those without the change indicated. Multivariable analyses were adjusted for age, gender, DRG weight, chronic kidney disease status, and *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for respiratory, gastrointestinal, malignant, and infectious diseases. Area under ROC curve for multivariable model. SCr, serum creatinine; OR, odds ratio; CI, confidence interval; ROC, receiver operating characteristic.
[b] Corresponding estimates of the multivariable relative risk (using the method of Zhang and Yu) 4.0, 6.0, 8.3, 11.8, 2.0, 4.2, 5.9, 6.9, and 6.0 from column top to bottom.

determinations. More than 10% of the sample (938) had 15 or more SCr determinations.

Patients with AKI were significantly older, had lower baseline creatinine clearances, and had higher severity of illness. The fraction of admissions with AKI differed significantly by ICD-9-CM category ($P < 0.0001$). The incidence of AKI (*e.g.*, increase in SCr ≥0.5 mg/dl) was highest among patients with cardiovascular diseases (20%); infectious diseases (18%); skin and soft tissue diseases (15%); endocrine, nutritional, and metabolic diseases (13%); respiratory diseases (12%); genitourinary diseases (12%); and injuries and poisoning (12%).

Mortality

Table 2 shows the unadjusted, age- and gender-adjusted, and multivariable-adjusted OR associated with AKI when AKI was determined by changes in SCr. Older patients and patients with CKD, higher disease severity, and admission diagnoses in the infectious disease, respiratory, gastrointestinal, and malignancy ICD-9-CM categories had an increased risk for death.

For the model that used a change in SCr of ≥0.5 mg/dl, the risks for death were higher for women than men ($P = 0.004$ for interaction) and for patients with *de novo* AKI compared with AKI superimposed on CKD ($P = 0.001$ for interaction). In models that used percentage change in SCr concentration (*e.g.*, ≥50% increase in SCr), these interactions were not statistically significant. Discrimination and calibration were similar for models that used nominal and percentage changes in SCr (Table 2).

The OR associated with AKI was independent of the proxy for prerenal *versus* other causes (Breslow-Day χ^2, $P = 0.56$). The OR associated with AKI was significantly increased across all major ICD-9-CM diagnosis categories. Compared with respiratory, infectious, gastrointestinal, malignant, and other diseases, the adjusted OR associated with AKI was attenuated in patients who were admitted with cardiovascular disease (OR 4.3; 95% confidence interval [CI], 2.7 to 6.8), although the AKI × cardiovascular disease interaction was of marginal statistical significance ($P = 0.02$). There were no other significant interactions by ICD-9-CM code. LOS (another proxy for severity) was not significantly associated with mortality when added to these models. Forced inclusion of LOS augmented the OR estimates for AKI.

We performed additional analyses to compare different incremental changes in SCr. Figure 2 shows the unadjusted, age-

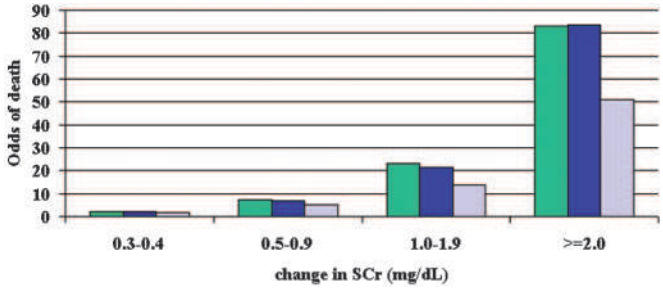


Figure 2. Mortality associated with change in serum creatinine. Green bars are unadjusted, blue bars are age and gender adjusted, and gray bars are multivariable adjusted. Multivariable analyses adjusted for age, gender, diagnosis-related group (DRG) weight, chronic kidney disease (CKD) status, and ICD-9-CM codes for respiratory, gastrointestinal, malignant, and infectious diseases; n = 1564, 885, 246, and 105 for change in SCr 0.3 to 0.4, 0.5 to 0.9, 1.0 to 1.9, and ≥2.0 mg/dl.

Table 3. LOS and costs associated with selected changes in SCr[a]

Criterion	Mean Unadjusted Increase in Total Cost ($)	Mean Adjusted (Marginal) Increase in Total Cost ($)
↑ SCr ≥ 0.3 mg/dl	$ 8,902	$ 4,886
↑ SCr ≥ 0.5 mg/dl	$12,656	$ 7,499
↑ SCr ≥ 1.0 mg/dl	$21,475	$13,200
↑ SCr ≥ 2.0 mg/dl	$33,161	$22,023
↑ SCr by 25%	$ 7,469	$ 3,721
↑ SCr by 50%	$10,125	$ 5,510
↑ SCr by 100%	$15,192	$ 8,999
↑ SCr by 50% to a minimum peak of 2.0 mg/dl	$19,517	$11,719
↑ SCr ≥ 0.5 mg/dl with baseline SCr < 2.0 mg/dl or ↑ SCr ≥ 1.0 mg/dl with baseline SCr ≥ 2.0 and < 5.0 mg/dl	$13,451	$ 7,982

[a]n = 2892, 1236, 351, 105, 4060, 1967, 714, 352, and 1160 for respective AKI criteria from denominator sample n = 9205. Results are relative to those without the change indicated. Multivariable analyses were adjusted for age, gender, DRG weight, and ICD-9-CM categories of cardiovascular, respiratory, malignant, and infectious diseases.

and gender-adjusted, and multivariable-adjusted OR associated with increases in SCr of 0.3 to 0.4, 0.5 to 0.9, 1.0 to 1.9, and ≥2.0 mg/dl, relative to patients with little or no change in SCr. It is noteworthy that even very small increases in SCr (0.3 to 0.4 mg/dl) were significantly associated with mortality (multivariable OR 1.7; 95% CI, 1.2 to 2.6).

We evaluated the risk for AKI in subcohorts of patients with three, four, and five or more SCr determinations (cohorts with corresponding overall mortality rates of 3.7, 4.3, and 4.7%, respectively). Compared with an adjusted OR of 6.5 (95% CI, 5.0 to 8.5) in the full cohort, corresponding OR for AKI were 6.4 (95% CI, 4.9 to 8.5), 6.5 (95% CI, 4.9 to 8.7), and 6.5 (95% CI, 4.8 to 8.9) in subcohorts of patients with three or more, four or more, and five or more SCr determinations.

Finally, we conducted analyses that considered changes in SCr over the initial 7 ± 2 d of hospitalization. This method of AKI classification decreased the number of patients with AKI (n = 1098 [12%], n = 242 [3%], and n = 45 [0.5%] for increases in SCr of ≥0.5, ≥1.0, and ≥2.0 mg/dl, respectively). The corresponding multivariable OR for death associated with AKI were 4.3 (95% CI, 3.3 to 5.6), 5.9 (95% CI, 4.1 to 8.5), and 5.9 (95% CI, 2.8 to 12.4).

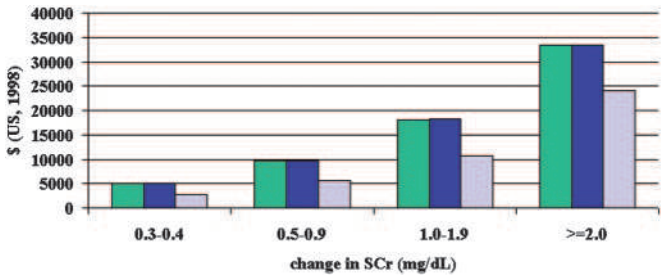


Figure 3. Mean hospital costs associated with changes in SCr. Green bars are unadjusted, blue bars are age and gender adjusted, and gray bars are multivariable adjusted. Multivariable analyses adjusted for age, gender, DRG weight, and ICD-9-CM codes for cardiovascular, respiratory, malignant, and infectious diseases; n = 1564, 885, 246, and 105 for change in SCr 0.3 to 0.4, 0.5 to 0.9, 1.0 to 1.9, and ≥2.0 mg/dl.

LOS

DRG weight was the strongest predictor of hospital LOS. Nevertheless, AKI was consistently associated with an independent increase in LOS. Using the ≥0.5 mg/dl increase in SCr criterion, we observed a 3.5-d increase in hospital LOS (P < 0.0001). In LOS models, there were no interactions among AKI, gender, and CKD. The models explained approximately 33% of the variance in LOS and were well fit. Larger increases in SCr were associated with longer relative increases in hospital LOS (*e.g.*, 5.4 and 7.9 d with ≥1.0- and ≥2.0-mg/dl increases in SCr, respectively). In addition to AKI, DRG weight, CKD, and gastrointestinal and malignant diseases were associated with longer LOS. When we restricted the analysis to patients who survived, the relative increases in LOS were magnified (3.6, 5.8, and 9.0 d, for increases in SCr ≥0.5, ≥1.0, and ≥2.0 mg/dl, respectively). When we considered only those individuals with AKI during the 7 ± 2 d of hospitalization, the corresponding relative increases in LOS were 2.1, 2.8, and 4.6 d.

Costs

Table 3 shows unadjusted and multivariable-adjusted mean costs for hospitalization with and without AKI using corresponding changes in SCr. As with LOS, the dominant predictor of total hospital costs was DRG weight. Multivariable models explained >40% of the variation in total hospital costs. Figure 3 shows the unadjusted, age- and gender-adjusted, and multivariable-adjusted costs associated with incremental changes in SCr concentration. The cost results were robust, even with further adjustment for LOS. When LOS was included, the models explained >65% of the variation in costs.

Discussion

Relatively few studies have examined the incidence and fewer have examined the consequences of hospital-acquired AKI. The oft-cited study by Hou *et al.* (1) reported an AKI

incidence of 5% (109 of 2216 medical and surgical patients). In that study, AKI was associated with decreased renal perfusion (42%), major surgery (18%), radiocontrast exposure (12%), and aminoglycoside administration (7%). Predictors of poor prognosis included oliguria and the severity of renal dysfunction (*i.e.*, increase in SCr of >3.0 mg/dl). Nash *et al.* (9) recently updated this report, demonstrating a similar risk factor profile and an AKI incidence of 7% among hospitalized patients.

Many studies have demonstrated an association between acute renal failure requiring dialysis and in-hospital mortality. Relatively few studies have examined the association between smaller changes in SCr and outcomes. Epidemiologic studies cannot provide a causal link between AKI and mortality. Acute kidney injury may be accompanied by acute lung injury and liver and other organ system failure, especially in critically ill patients. However, published studies have demonstrated a consistently high relative risk associated with AKI despite adjustment for comorbid conditions and severity of illness.

Levy *et al.* (10) compared a Yale-New Haven Hospital cohort of 183 patients with radiocontrast-associated AKI and 174 patients who were matched for age and baseline SCr and underwent similar diagnostic procedures without developing AKI. The mortality rate was 34% in patients with AKI *versus* 7% in patients without AKI. Adjusting for differences in comorbidity, the odds of death were increased 5.5-fold in the AKI group. We have previously shown a 6.3-fold increase in the odds of death among 643 patients with amphotericin B–associated AKI (11).

Several other groups have shown an association between very small changes in SCr and outcomes. Krumholz *et al.* (12,13) explored this issue in elderly individuals who were hospitalized with congestive heart failure, for whom small changes in SCr concentration have been associated with increased mortality and extended (>10 d) LOS. Recently, Lassnigg *et al.* (14) showed a two-fold increase in the risk for death for patients who experienced no change or a small increase (<0.5 mg/dl) in SCr 48 h after cardiothoracic surgery compared with patients who experienced a small decline in SCr during the same time frame. In a similar population, Loef *et al.* (15) showed an association between a 25% increase in SCr during the first postoperative week and short- and long-term (>8 yr) mortality. Our study extends these findings from previously published reports. We studied a larger cohort with a wide variety of reasons for hospitalization, evaluated associations with several perturbations in SCr, and evaluated associations with LOS and costs.

In this study, although the associations with relatively large changes in SCr (*e.g.*, ≥2.0 mg/dl) were most striking, large changes in SCr were relatively rare. In contrast, >30% of patients with two or more SCr determinations experienced an increase in SCr of 0.3 to 0.4 mg/dl. These individuals experienced a 70% increase in the risk for death relative to patients with little or no change in SCr.

Because AKI has no uniform definition (and, consequently, no accurate estimate of incidence), we previously had little information on which to evaluate the public health or financial impact of AKI relative to other serious conditions. Although we estimated a considerable increase in cost associated with AKI in amphotericin B–treated individuals (approximately $30,000 per episode), this analysis considered an extreme clinical scenario and applied a single, arbitrary definition of AKI (50% increase in SCr to at least 2.0 mg/dl) (11). In contrast, the broad-based population that was evaluated in our study allows for estimation of the burden of AKI. The total annualized hospital costs for the 9205 patients with two or more SCr determinations was approximately $148,150,000, $13,167,000 (9%) of which was attributed to AKI using the ≥0.5-mg/dl change in SCr definition. This would represent roughly 5% of overall hospital costs when considering all admissions, including individuals with zero or one SCr determination. The National Center for Health Statistics estimated 122 hospital discharges per 1000 noninstitutionalized persons in the United States in 2001 (http://www.cdc.gov/nchs), corresponding to roughly 34,000,000 admissions per year. If we were to estimate conservatively the incidence of hospital-acquired AKI at 5% and consider average costs 20% below those observed here, then the estimated annual health care expenditures that were attributable to hospital-acquired AKI would exceed $10 billion.

This study has several strengths. The findings of increased mortality, LOS, and costs were robust across age, gender, CKD and non-CKD, and ICD-9-CM group categories. A single laboratory was used, limiting interlaboratory error and misclassification. This study also has several important limitations. First, the method of estimating baseline and peak SCr may have overestimated the proportion of patients who were classified with AKI. However, such misclassification would have biased the associations among AKI, mortality, LOS, and costs toward the null so that the effect estimates presented here may be conservative. Second, we had relatively few available covariates. Nevertheless, the covariates that were applied in the analyses (DRG weight and ICD-9-CM codes) are commonly used risk adjusters that explained a large fraction of the variance. Whether adverse outcomes can be attributed directly to AKI or residual confounding by severity of disease is unknown. Although residual confounding could lessen the magnitude of the risk estimates, additional covariates would be extremely unlikely to extinguish OR in the 5 to 10 range. Fourth, we had no data on the physiology of AKI and used proxies to attempt to distinguish prerenal from other causes of AKI. In future studies, we could refine the prerenal *versus* other classification with additional physiologic data (*e.g.*, BP, urine output, fractional excretion of sodium). Fifth, biochemical measures that are more sensitive to change in GFR (16) or novel imaging modalities (17) may prove to be more effective markers of early AKI. Finally, because the data were obtained in an urban tertiary care hospital, the results may not be fully generalizable to the universe of hospitalized patients.

In summary, AKI is associated with significantly increased mortality, LOS, and costs across a broad spectrum of conditions. Moreover, outcomes are related directly to the severity of AKI, whether characterized by nominal or percentage changes in serum creatinine. Although less obvious to clinicians than severe AKI requiring dialysis, non–dialysis-requiring AKI may be of equal or greater importance from a public health perspective. Prevention and effective treatment of hospital-acquired AKI should be a national priority.

Acknowledgments

This study was presented in abstract form at the 2003 American Society of Nephrology meetings; November 2003; San Diego, CA.

Appendix

Prerenal ICD-9-CM Diagnosis Codes and Medications

ICD-9-CM Code	Description
276	Volume depletion, hypovolemia, dehydration, hyperosmolality or hypernatremia, hypo-osmolality, or hyponatremia
428	Heart failure
459	Hemorrhage, unspecified
531–534	Peptic ulcer disease
571–572	Chronic liver disease
578	Gastrointestinal hemorrhage
785	Shock, tachycardia

Class	Specific Agents
Diuretics[a]	Acetazolamide
	Amiloride
	Bumetanide
	Ethacrynic acid
	Furosemide
	Hydrodiuril
	Hydrochlorothiazide
	Indipamide
	Mannitol
	Metolazone
	Spironolactone
	Torsemide
	Triamterene
Colloids	Albumin
	Dextran
	Hetastarch
Drugs for heart failure	Digoxin
	Dobutamine
	Milrinone
Nonsteroidal anti-inflammatory drugs	Diclofenac
	Fenoprofen
	Flurbiprofen
	Ibuprofen
	Indomethacin
	Ketoprofen
	Ketorolac
	Naproxen
	Piroxicam
	Sulindac
	Tolmentin
Calcineurin inhibitors	Cyclosporin
	Tacrolimus

[a]Including combination diuretic agents.

References

1. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT: Hospital-acquired renal insufficiency: A prospective study. *Am J Med* 74: 243–248, 1983
2. Shusterman N, Strom BL, Murray TG, Morrison G, West SL, Maislin G: Risk factors and outcome of hospital-acquired acute renal failure. Clinical epidemiologic study. *Am J Med* 83: 65–71, 1987
3. Chertow GM, Lee J, Kuperman GJ, Burdick E, Horsky J, Seger DL, Lee R, Mekala A, Song J, Komaroff AL, Bates DW: Guided medication dosing for inpatients with renal insufficiency. *JAMA* 286: 2839–2844, 2001
4. Edwards N, Honemann D, Burley D, Navarro M: Refinement of the Medicare diagnosis-related groups to incorporate a measure of severity. *Health Care Financ Rev* 16: 45–64, 1994
5. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
6. Zhang J, Yu KF: What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 280: 1690–1691, 1998
7. Hanley JA, McNeil BJ: The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 143: 29–36, 1982
8. Lemeshow S, Hosmer DW Jr: A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol* 115: 92–106, 1982
9. Nash K, Hafeez A, Hou S: Hospital-acquired renal insufficiency. *Am J Kidney Dis* 39: 930–936, 2002
10. Levy EM, Viscoli CM, Horwitz RI: Effect of acute renal failure on mortality. A cohort analysis. *JAMA* 275: 1489–1494, 1996
11. Bates DW, Su L, Yu DT, Chertow GM, Seger DL, Gomes DRJ, Platt R: The mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin Infect Dis* 32: 686–693, 2001
12. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, O'Connor CM, Rich MW, Stevenson LW, Young J, Krumholz HM: The prognostic importance of different definitions of worsening renal function in congestive heart failure. *J Card Fail* 8: 136–141, 2002
13. Smith GL, Vaccarino V, Kosiborod M, Lichtman JH, Cheng S, Watnick SG, Krumholz HM: Worsening renal function: What is a clinically meaningful change in creatinine during hospitalization with heart failure? *J Card Fail* 9: 13–25, 2003
14. Lassnigg A, Schmidlin D, Mouhieddine M, Bachmann LM, Druml W, Bauer P, Hiesmayr M: Minimal changes of serum creatinine predict prognosis in patients after cardiothoracic surgery: A prospective cohort study. *J Am Soc Nephrol* 15: 1697–1705, 2004
15. Loef BG, Epema AH, Smilde TD, Henning RH, Ebels T, Navis G, Stegeman CA: Immediate postoperative renal function deterioration in cardiac surgical patients predicts in-hospital mortality and long-term survival. *J Am Soc Nephrol* 16: 195–200, 2005
16. Dharnidharka VR, Kwon C, Stevens G: Serum cystatin C is superior to serum creatinine as a marker of kidney function: A meta-analysis. *Am J Kidney Dis* 40: 221–226, 2002
17. Dagher PC, Herget-Rosenthal S, Ruehm SG, Jo SK, Star RA, Agarwal R, Molitoris BA: Newly developed techniques to study and diagnose acute renal failure. *J Am Soc Nephrol* 14: 2188–2198, 2003

See related editorial, "Towards a Definition and Classification of Acute Kidney Injury," on pages 3149–3150.

THANK YOU FOR YOUR ORDER

Thank you for your recent purchase. If you need further assistance, please contact Customer Service at cs-support@infotrieve.eu. Please include the Request ID, so we can better assist you.

This is not an invoice.

CUSTOMER INFORMATION

Ordered For:	Corinne Plonquet
Company:	bioMérieux
Client ID:	8983
Address:	bioMérieux Service Info Doc
	Chemin de l'Orme
	Marcy l'Etoile, 69280
Country:	France
Phone:	33 4 78 87 5363
Fax:	33 4 78 87 2124
Email:	corinne.plonquet@biomerieux.com

ORDER INFORMATION

Request ID:	8718784
Ordered For:	Corinne Plonquet
Ordered For Email:	corinne.plonquet@biomerieux.com
Ordered:	28.09.2017 09:52
Deliver Via:	Email (PDF)
Delivery Address:	nathalie.vernay@biomerieux.com
Tracking Info.:	140820/INFODOC/NV/ZIMMER L
	140820

DOCUMENT INFORMATION

Std. Num.:	15535592	Type:	Doc Del (Journal Article)
Publication:	Journal of Hospital Medicine	Copies:	1
Publisher:		Urgency:	Normal
Vol(Iss) Pg:	12 (2) p.70-76	Genre:	Journal Article
Date	2/1/2017	Total Fee:	48,87 €
Title:	Cost of acute kidney injury in hospitalized patients		
Author(s):	Silver, Samuel A; Long, Jin; Zheng, Yuanchao; Chertow, Glenn M		

Usage: 1 copy may be used for the following purpose: "Internal General Business Use"

Cost of Acute Kidney Injury in Hospitalized Patients

Samuel A. Silver, MD, MSc[1,2*], Jin Long, PhD[1], Yuanchao Zheng, MS[1], Glenn M. Chertow, MD, MPH[1]

[1]Division of Nephrology, Stanford University School of Medicine, Palo Alto, California; [2]Division of Nephrology, University of Toronto, Toronto, Canada.

BACKGROUND: The economic burden of acute kidney injury (AKI) is not well understood.

OBJECTIVE: To estimate the effects of AKI on hospitalization costs and length of stay (LOS).

DESIGN: Using data from the 2012 National Inpatient Sample, we compared hospitalization costs and LOS with and without AKI. We used a generalized linear model with a gamma distribution and a log link fitted to AKI to adjust for demographics, hospital differences, and comorbidities.

SETTING: United States

PATIENTS: 29,763,649 adult hospitalizations without end-stage renal disease.

EXPOSURE: AKI determined using International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes.

MEASUREMENTS: Hospitalization costs and LOS.

RESULTS: AKI was associated with an increase in hospitalization costs of $7933 (95% confidence interval [CI], $7608-$8258) and an increase in LOS of 3.2 (95% CI, 3.2-3.3) days compared to patients without AKI. When adjusted for patient and hospital characteristics, the associated increase in costs was $1795 (95% CI, $1692-$1899) and in LOS, it was 1.1 (95% CI, 1.1-1.1) days. Corresponding results among patients hospitalized with AKI requiring dialysis were $42,077 (95% CI, $39,820-$44,335) and 11.5 (95% CI, 11.2-11.8) days and $11,016 (95% CI, $10,468-$11,564) and 3.9 (95% CI, 3.8-4.1) days. AKI was associated with higher hospitalization costs than myocardial infarction and gastrointestinal bleeding, and costs were comparable to those for stroke, pancreatitis, and pneumonia.

CONCLUSIONS: In the United States, AKI is associated with excess hospitalization costs and prolonged LOS. The economic burden of AKI warrants further attention from hospitals and policymakers to enhance processes of care and develop novel treatment strategies. *Journal of Hospital Medicine* 2017;12:70-76. © Society of Hospital Medicine

Acute kidney injury (AKI) is a common complication that affects as many as 20% of hospitalized patients, depending on the definition employed.[1-3] AKI is associated with significant morbidity and mortality; hospitalized patients with AKI require more investigations and medications,[4] develop more postoperative complications,[5] and spend more time in the intensive care unit than do patients without AKI.[6] Inhospital mortality for patients with AKI has recently been estimated between 20-25%,[3,7] and critically ill patients with AKI requiring dialysis experience mortality rates in excess of 50%.[8,9] AKI and its accompanying complications may continue to rise, as the incidence of AKI and AKI requiring dialysis is increasing at a rate of approximately 10% per year.[10-12]

Owing to poor outcomes and rising incidence, AKI has emerged as a major public health concern with high human and financial costs; however, the costs related to AKI have been excluded from recent United States Renal Data System estimates.[13] Most studies that have explored the costs related to hospitalizations complicated by AKI have been single-center or local studies in specialized patient populations.[4,5,14-18] Very few studies have used data after the year 2000, when the incidence of AKI began to increase, likely related to a combination of patient age, comorbidity burden, sepsis, heart failure, and nephrotoxic medications.[10,11] Moreover, it is unclear which patient and hospital characteristics contribute most to the cost of an AKI hospitalization, and how the costs of AKI compare to those for other acute medical conditions. Such information is important for hospitals, policymakers, and researchers to target prevention and management strategies for high-risk and high-cost patient groups.

The main objectives of this study were to determine the costs of AKI-related hospitalization, and patient and hospital factors associated with these costs. We hypothesized that costs related to AKI would add several thousand dollars to each hospitalization and would eclipse the cost of many higher profile acute medical conditions.

METHODS

Study Population

We extracted data from the National Inpatient Sample (NIS), a nationally representative administrative database of hospitalizations in the United States (U.S.) created by the Agency for Healthcare Research and Quality as part of the Healthcare Cost and Utilization Project.[19] The NIS is the largest all-payer inpatient-care database, and contains a 20% stratified sample of yearly discharge data from short-term, non-Federal, nonrehabilitation hospitals. Data are

***Address for correspondence and reprint requests**: Samuel A. Silver, Stanford University School of Medicine, Division of Nephrology, 1070 Arastradero Road, Palo Alto, CA, 94304; Telephone: 650-504-0030; Fax: 650-721-1443; E-mail: sam.silver@utoronto.ca

Additional Supporting Information may be found in the online version of this article.

Received: May 9, 2016; **Revised**: July 13, 2016; **Accepted**: July 24, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2683

stratified according to geographic region, location (urban/rural), teaching status, ownership, and hospital bed number. Each hospitalization is treated as an individual entry in the database (ie, individual patients who are hospitalized multiple times may be present in the NIS multiple times). The NIS includes demographic variables, diagnoses, procedures, LOS, and hospital charges. Sample weights are provided to allow for the generation of national estimates, along with information necessary to calculate the variance of estimates.

We utilized the 2012 NIS subset, the most recent year available at the time of data analysis. The 2012 NIS subset contained administrative data from over 7 million hospitalizations, representing more than 4000 hospitals, 44 states, and 95% of the US population. We excluded patients under 18 years of age and patients with end-stage renal disease (ESRD). We identified patients with ESRD using diagnosis codes and procedure codes from the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, Supplemental Table 1). We also excluded hospitalizations with an ICD-9 diagnosis or procedure code for dialysis but without a diagnosis code for AKI, assuming that these patients were treated with dialysis for ESRD. We and others have used this approach,[11,20,21] which has been shown to produce high sensitivity and specificity, as well as high positive and negative predictive values (all equal to or greater than 90%) for differentiating dialysis-requiring AKI (AKI-D) from chronic dialysis.[21]

Primary and Secondary Exposures

Episodes of AKI were identified using the ICD-9 diagnosis code 584.x. This administrative code for AKI has low sensitivity, but high specificity of approximately 99%: our cohort includes few false positives, and identifies a more severe spectrum of AKI compared to serum creatinine criteria.[21,22] For example, the median (25th, 75th percentile) change in serum creatinine from baseline is estimated at 1.2 (0.7 to 2.1) mg/dL compared with 0.2 (0.1 to 0.2) mg/dL for patients without an administrative code for AKI.[21] We defined AKI-D as the presence of an AKI diagnosis code and a diagnosis or procedure code for dialysis. This algorithm for AKI-D has been shown to yield high sensitivity and specificity.[21] Secondary exposures included several acute medical conditions (myocardial infarction, stroke, venous thromboembolic disease, gastrointestinal bleed, acute pancreatitis, sepsis, and pneumonia) whose incremental costs and LOS could be compared to AKI (Supplemental Table 1).

Covariates

We assessed patient comorbidities from the 25 diagnoses listed in the NIS for each record (Supplemental Table 1). Hospital-level variables included geographic region, bed number, and teaching status using predetermined NIS definitions.[19]

Outcomes

The primary outcome was the inpatient cost of each hospital record in 2012 dollars. We estimated costs from the total

TABLE 1. Characteristics of the Cohort

Characteristic, %	No AKI (n = 26,732,623)	AKI[a] (n = 3,031,026)	AKI-D (n = 106,515)
Age, mean (SD)	55.8 (0.1)	69.0 (0.1)	63.3 (0.2)
Sex			
Male	38.9%	52.8%	58.2%
Female	61.1%	47.3%	41.8%
Hospital teaching status			
Rural	12.1%	9.8%	5.2%
Urban nonteaching	38.7%	38.8%	37.0%
Urban teaching	49.2%	51.4%	57.8%
Hospital region			
Northeast	19.7%	18.8%	16.1%
West	18.9%	18.4%	21.3%
Midwest	22.9%	22.7%	22.4%
South	38.5%	40.1%	40.2%
Hospital bed number			
Small	14.5%	12.8%	9.2%
Medium	26.5%	26.5%	24.2%
Large	59.1%	60.7%	66.7%
Acute medical conditions			
Myocardial infarction	2.6%	6.7%	11.0%
Stroke	3.0%	3.4%	4.1%
Venous thromboembolic disease	2.1%	3.9%	7.3%
Gastrointestinal bleed	2.2%	5.3%	8.9%
Acute pancreatitis	1.3%	1.9%	4.4%
Sepsis	3.6%	20.2%	43.0%
Pneumonia	6.6%	16.1%	27.0%
Chronic comorbidities			
Cancer	9.0%	12.7%	14.7%
Chronic kidney disease	7.1%	46.2%	51.3%
Congestive heart failure	11.8%	34.0%	40.5%
Dementia	5.4%	11.9%	3.7%
Diabetes	21.3%	41.6%	41.2%
Human immunodeficiency virus	0.3%	0.7%	1.0%
Hypertension	47.4%	73.0%	66.0%
Chronic obstructive pulmonary disease	12.7%	20.0%	18.0%
Peripheral vascular disease	5.4%	10.8%	11.6%
Hospital procedures			
Intravenous contrast	4.9%	5.4%	8.7%
Blood product transfusion	6.8%	17.8%	40.8%
Mechanical ventilation	2.2%	11.2%	43.4%
Noninvasive ventilation	1.5%	4.2%	8.0%
Cardiopulmonary resuscitation	0.2%	1.3%	5.6%
Left ventricular assist device	0.0%	0.1%	0.5%
Extracorporeal membrane oxygenation	0.0%	0.1%	0.4%
Echocardiogram	2.3%	4.7%	8.0%
Coronary angiogram	4.1%	4.7%	7.7%
Percutaneous transluminal coronary angioplasty	1.8%	1.4%	2.0%
Cardiopulmonary bypass	0.8%	1.3%	3.7%
Coronary artery bypass grafting	0.6%	1.1%	2.3%
Heart valve surgery	0.3%	0.7%	2.1%
Abdominal aortic aneurysm repair	0.2%	0.2%	0.8%
Carotid endarterectomy	0.4%	0.1%	0.2%
Peripheral vascular surgery	0.6%	0.8%	1.7%

[a]The AKI group includes patients with AKI-D.

NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis.

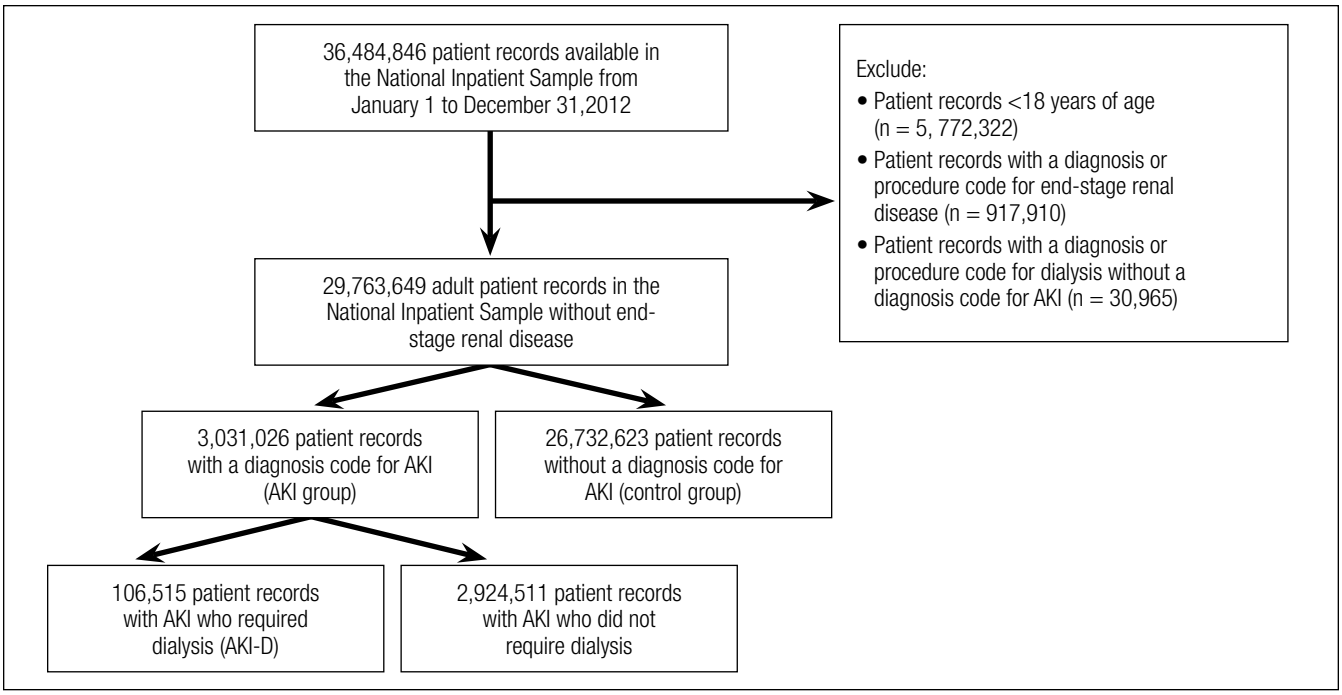


FIG. 1. Inclusion and exclusion criteria used to define a cohort of patients with and without AKI
NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis.

charge for each hospitalization by applying hospital-specific charge-to-cost ratios. The NIS obtained cost information from the hospital accounting reports collected by the Centers for Medicare and Medicaid Services.[19] The secondary outcome was hospital LOS.

Statistical Analysis

We summarized baseline characteristics of the study participants using descriptive statistics. Normally distributed continuous variables were expressed as mean (standard deviation [SD]), and nonparametric continuous variables were expressed as median (25th, 75th percentile). Categorical variables were expressed as proportions. We calculated the mean increase in cost and LOS of each hospital record, comparing hospital records with AKI and AKI-D to hospital records without AKI. We took the same approach when examining incremental costs and LOS associated with other acute medical conditions. Due to the skewness of cost and LOS data, we used a generalized linear model with a gamma distribution and a log link fitted to the primary or secondary exposure to obtain the unadjusted mean increase in cost and LOS.[23,24] We incorporated demographics, hospital differences, comorbidities (including AKI when it was compared to the other acute medical conditions), and procedures into the generalized linear model to calculate the adjusted mean increase in cost and LOS. This method also provides the adjusted percentage change in hospital costs and LOS from the estimated beta-coefficients in the multivariable model. We calculated the proportion of variation in the outcomes explained by the generalized linear models using pseudo R-squared measured by the Kullback-Leibler divergence.[25] As a companion analysis, we repeated estimates for AKI-D when dialysis was initiated within 7 days of hospital admission because subsequent events during the hospital stay would more likely be attributable to the AKI episode. All analyses presented account for the NIS survey design (weighting and stratification) and subpopulation measurements to generate national estimates. We created the cohort using the Statistical Analysis System software, version 9.4 (SAS Institute, Cary, North Carolina) and conducted the analyses using StataMP, version 14.0 (Stata Corporation, College Station, Texas).

RESULTS

Patient Characteristics

Between January 1 and December 31, 2012, there were 36,484,846 hospitalization records available in the NIS; 948,875 adult records (2.6%) were classified as having ESRD and 29,763,649 (81.6%) were included in the final cohort. Within the final cohort, 3,031,026 (10.2%) hospitalizations were complicated by AKI, of which 106,515 (3.5%) required dialysis (corresponding to 0.36% of the analytic cohort) (Figure 1).

Compared to patients without AKI, patients with AKI were older (69.0 years vs. 55.8 years) and a larger proportion were male (52.8% vs. 38.9%). All measured comorbidities were more prevalent in patients with AKI. Patients with AKI also underwent more hospital procedures than patients without AKI (Table 1).

Hospitalization Costs

Figures 2A and 2B show unadjusted and multivariable-adjusted mean increases in cost of a hospitalization with AKI

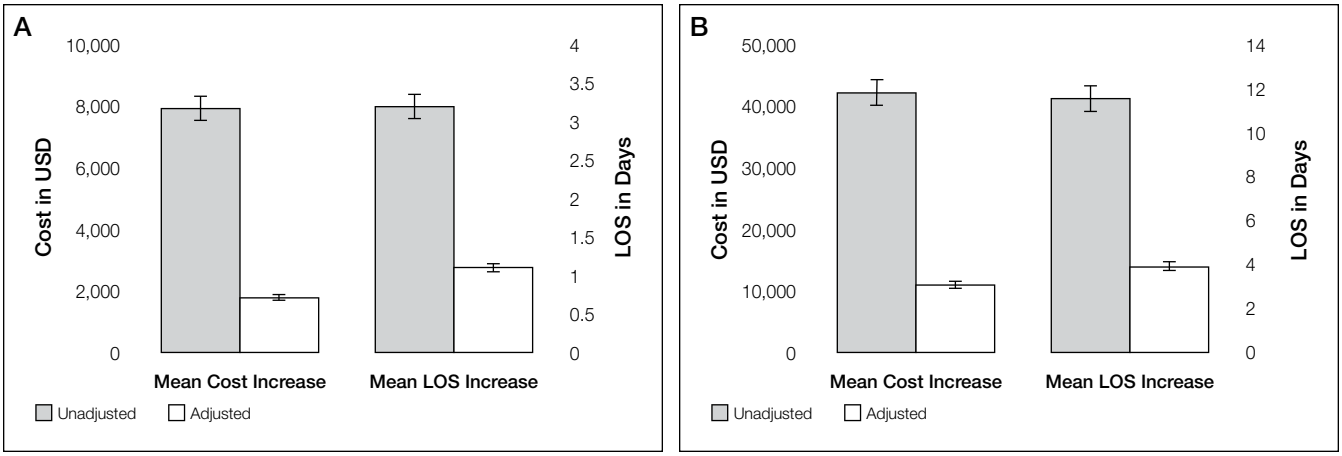


FIG. 2. (A) Mean increase in cost and LOS per hospital admission of AKI compared to a hospital admission without AKI. Costs increases are in 2012 dollars. White bars are adjusted for the demographic factors, hospital differences, comorbidities, and procedures listed in Table 1. Error bars represent the 95% confidence intervals. The multivariable model explained 67% of the variation in total hospital costs and 47% of the variation in LOS. (B) Mean increase in cost and LOS per hospital admission of AKI-D compared to a hospital admission without AKI. Cost increases are in 2012 dollars. White bars are adjusted for the demographic factors, hospital differences, comorbidities, and procedures listed in Table 1. Error bars represent the 95% confidence intervals. The multivariable model explained 53% of the variation in total hospital costs and 64% of the variation in LOS.

NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis; LOS, length of stay.

and AKI-D compared to a hospitalization without AKI. Extrapolating to the 2012 population estimates in Table 1 for AKI and AKI-D, increases in cost related to AKI ranged from $24.0 billion (unadjusted) to $5.4 billion (adjusted) and for AKI-D ranged from $4.5 billion (unadjusted) to $1.2 billion (adjusted).

Mean increases in the cost of a hospitalization for AKI exceeded costs associated with other acute medical conditions such as myocardial infarction and gastrointestinal bleeding. Costs associated with AKI were similar to hospitalizations for stroke, acute pancreatitis, and pneumonia. Costs of AKI-D exceeded those related to sepsis and venous thromboembolic disease (Table 2). AKI was the most common of the acute medical conditions examined (3,031,026 patients, 10.2%).

Major drivers of cost included urban and teaching hospitals, hospitals in the Southern US (relative to other regions), hospitals with a larger number of beds, most acute medical conditions, cancer, and hospital procedures. Older age was associated with higher costs with non-AKI hospitalizations but lower costs with AKI hospitalizations (0.67% vs. -0.44%, per year of age). Determinants of hospital costs are shown in Supplemental Table 2. Generally, hospital procedures accounted for the largest relative increases in cost.

Length of Stay

Figures 2A and 2B show unadjusted and multivariable-adjusted mean increases in LOS for a hospitalization with AKI and AKI-D compared to a hospitalization without AKI. Extrapolating to the 2012 population estimates in Table 1 for AKI and AKI-D, increases in LOS related to AKI ranged

TABLE 2. Mean Increase in Cost and LOS per Hospital Admission of AKI and Other Acute Medical Conditions

Acute Medical Condition	Prevalence, No. (%)	Adjusted Mean Cost Increase in 2012 US Dollars (95% CI)[a]	Adjusted Mean Length of Stay Increase in Days (95% CI)[a]
AKI[b]	3,031,026 (10.2)	1795 (1692, 1899)	1.1 (1.1, 1.1)
AKI requiring dialysis (AKI-D)	106,515 (0.4)	11016 (10468, 11564)	3.9 (3.8,4.1)
Myocardial infarction	901,276 (3.0)	14 (-91, 119)	0.1 (0.1, 0.2)
Stroke	901,227 (3.0)	1427 (1281,1573)	0.1 (0, 0.1)
Venous thromboembolic disease	677,202 (2.3)	3782 (3611, 3953)	2.3 (2.2, 2.3)
Gastrointestinal bleed	743,692 (2.5)	-860 (-961, -759)	0 (0, 0.1)
Acute pancreatitis	413,827 (1.4)	1802 (1676,1929)	1.1 (1.1, 1.2)
Sepsis	1,577,242 (5.3)	4882 (4696, 5068)	2.1 (2.1, 2.2)
Pneumonia	2,246,687 (7.5)	1705 (1584,1825)	1.2 (1.2, 1.2)

[a]For each comparison, the reference group is patients without the condition of interest (for AKI-D, the reference group is patients without AKI). All estimates are adjusted for the demographic factors, hospital differences, comorbidities, and procedures listed in Table 1. Non-AKI conditions are also adjusted for AKI.

[b]The AKI group includes patients with AKI-D.

NOTE: Abbreviations: AKI, acute kidney injury; AKI-D, acute kidney injury requiring dialysis; CI, confidence interval; LOS, length of stay.

from 9.8 million days (unadjusted) to 3.3 million days (adjusted) and for AKI-D ranged from 1.2 million days (unadjusted) to 0.4 million days (adjusted).

When compared to other acute medical conditions, the mean increase in LOS of an AKI hospitalization resembled the order for mean increases in cost (Table 2). Major drivers of LOS also resembled drivers of costs, with the exception of some common cardiovascular procedures (percutaneous transluminal coronary angioplasty, abdominal aortic aneurysm repair, and carotid endarterectomy) that were associated only with prolonged LOS in the AKI and AKI-D groups (Supplemental Table 3).

Companion Analysis

In an analysis of 78,220 patients who developed AKI-D within 7 days of hospital admission (73% of AKI-D cases), increases in cost ranged from $32,133 (unadjusted) to $8594 (adjusted) and increases in LOS ranged from 8.4 days (unadjusted) to 2.9 days (adjusted) compared to patients without AKI.

DISCUSSION

We found that hospitalizations complicated by AKI were more costly—between $1800 and $7900—than hospitalizations that did not involve AKI, which indicates that AKI could be responsible for billions of dollars of annual healthcare spending. Relative to several other acute medical conditions, AKI was more common and expensive; when AKI was severe enough to require dialysis, costs of AKI exceeded all other acute medical conditions by a large margin.

Several single-center and regional studies have highlighted the association of AKI with hospital costs and LOS. In a single-center study conducted in the late 1990s, Chertow et al[14] described mean cost increases between $4900 (adjusted) and $8900 (unadjusted) and LOS increases of 3.5 days (adjusted) using serum creatinine criteria to define AKI.[14] These higher adjusted estimates may result because their multivariable models did not adjust for several major determinants of cost, including several procedures and hospital-level variables. A study at the same academic center in 2010, which adjusted for some procedures, found AKI was associated with a 2.8-day increase in LOS and a $7082 increase in costs;[2] however, this study also could not adjust for hospital-level variables because of the single-center design. Fischer et al[15] were able to adjust for hospital teaching status in their study that included 23 local hospitals. Similar to our results, teaching hospitals were associated with an approximately 17% increase in cost compared to nonacademic hospitals. However, this study excluded patients who required critical care or mechanical ventilation, which limits the generalizability of their cost estimates. Another limitation of these 3 studies is that they were all conducted in Massachusetts. Beyond the US, the economic burden of AKI has been studied in England where the annual cost of AKI-related inpatient care has been estimated at $1.4 billion.[16] In addition to incomplete procedure and hospital-level adjustment, this study is limited by its ascertainment of AKI and costs, which was extrapolated from 1 hospital region to the rest of England.

Our study adds to the existing evidence in a number of ways. It uses nationally representative data to determine a lower and an upper limit of increases in cost and LOS attributable to AKI. The adjusted value is likely overly conservative; it minimizes the influence of events that are attributable to AKI and does not account for complications that may be caused by, or otherwise related to, AKI. The unadjusted value is likely an overestimate, attributing events during an AKI hospitalization to the AKI episode, even if they precede AKI. In clinical practice, most patients fall between these 2 extremes. Therefore, we suggest using the adjusted and unadjusted estimates to provide a range of the cost and LOS increases that are attributable to AKI. This interpretation is also supported by the companion analysis that minimizes the effect of pre-AKI events, where the unadjusted cost and LOS estimates for AKI-D occurring early during a hospitalization fell between the unadjusted and adjusted estimates for the main AKI-D analysis. Therefore, our data suggest that each hospitalization complicated by AKI is associated with a cost increase between $1800 and $7900 and an LOS increase between 1.1 days and 3.2 days. Not surprisingly, the burden of AKI-D was more pronounced with a cost increase between $11,000 and $42,100 and an LOS increase between 3.9 days and 11.5 days.

Unlike previous studies, these analyses are fully adjusted for procedures and multiple hospital-level variables (such as teaching status, region, and bed number). These adjustments are important because procedures account for much of the incremental cost and LOS associated with AKI, and each hospital-level variable may increase the cost and LOS of an AKI hospitalization by 10% to 25% (Supplemental Tables 2 and 3). Even though the relative increases in cost and LOS associated with different comorbidities and procedures were largely similar between patients with and without AKI, the absolute increases were usually larger in patients with AKI rather than without AKI because of their higher baseline estimates. We also observed that each year of age was associated with increased costs in patients without AKI, but decreased costs in patients with AKI. We suspect this difference is due to the lesser (and ultimately less costly) injury required to induce AKI in elderly patients who have less physiologic reserve.[26] Moreover, we placed the burden of AKI in relation to other acute medical conditions, where its total estimated annual costs of $5.4 billion were exceeded only by the $7.7 billion attributed to sepsis.

Our results emphasize that AKI is an important contributor to hospital costs and LOS. Despite these consequences, there have been very few innovations in the prevention and management of AKI over the last decade.[27,28] The primary treatment for severe AKI remains dialysis, and recent clinical trials suggest that we may have reached a dose plateau in the value of dialytic therapy.[8,29] Several opportunities, such as advances in basic science and clinical care, may improve the care of patients with AKI. Translational research chal-

lenges in AKI have been reviewed, with treatment strategies that include hemodynamic, inflammatory, and regenerative mechanisms.[28, 30] In a recent report from the National Confidential Enquiry into Patient Outcome and Death in the United Kingdom, 30% of AKI episodes that occurred inhospital were preventable, and only 50% of patients with AKI were deemed to have received good care.[31] Our results suggest that even small progress in these areas could yield significant cost savings. One starting point suggested by our findings is a better understanding of the reasons underlying the association between hospital-level variables and differences in cost and LOS. Notably, there have been few efforts to improve AKI care processes on the same scale as sepsis,[32] myocardial infarction,[33,34] stroke,[35] and venous thromboembolic disease.[36]

Strengths of this study include cost and LOS estimates of AKI from different hospitals across the US, including academic and community institutions. As a result, our study is significantly larger and more representative of the US population than previously published studies. Moreover, we utilized data from 2012, which accounts for the increasing incidence of AKI and recent advances in critical care medicine. We were also able to adjust for comorbid conditions, procedures, severity of illness, and hospital-level variables, which provide a conservative lower limit of the burden of AKI on hospitalized patients.

Our study has limitations. First, we used administrative codes to identify patients with AKI. The low sensitivity of these codes suggests that many patients with milder forms of AKI were probably not coded as such. Accordingly, our findings should be generally applicable to patients with moderate to severe AKI rather than to those with mild AKI.[21,22] Second, the NIS lacks granularity on the details and sequence of events during a hospitalization. As a result, we could not determine the timing of an AKI episode during a hospitalization or whether a diagnosis or procedure was the cause or consequence of an AKI episode (ie, day 1 as the reason for admission vs. day 20 as a complication of surgery). Both the timing and cause of an AKI episode may influence cost and LOS, which should be considered when applying our results to patient care. We did not attempt to estimate the costs associated with comorbidities such as congestive heart failure and chronic obstructive pulmonary disease because we could not determine the acuity of disease in the NIS. Third, despite our efforts, residual confounding is likely, especially since administrative data limit our ability to capture the severity of comorbid conditions and the underlying illness. Fourth, the NIS does not contain individual patient identifiers, so multiple hospitalizations from the same patient may be represented.

Even our most conservative estimates still attribute $5.4 billion and 3.3 million hospital-days to AKI in 2012. These findings highlight the need for hospitals, policymakers, and researchers to recognize the economic burden of AKI. Future work should focus on understanding hospital-level differences in AKI care and the effect on patient morbidity and mortality. National and hospital-wide quality improvement programs are also needed. Such initiatives have commenced in the United Kingdom,[37] and similar efforts are needed in North America to develop and coordinate cost-effective strategies to care for patients with AKI.

Disclosures: Samuel A. Silver, MD, MSc, is supported by a Kidney Research Scientist Core Education and National Training Program Post-Doctoral Fellowship (co-funded by the Kidney Foundation of Canada, Canadian Society of Nephrology, and Canadian Institutes of Health Research). Glenn M. Chertow, MD, MPH, is supported by a K24 mid-career mentoring award from NIDDK (K24 DK085446). These funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, or approval of the manuscript; or decision to submit the manuscript for publication. The authors report no financial conflicts of interest.

References

1. Waikar SS, Liu KD, Chertow GM. Diagnosis, epidemiology and outcomes of acute kidney injury. *Clin J Am Soc Nephrol*. 2008;3:844-861.
2. Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin J Am Soc Nephrol*. 2014;9:12-20.
3. Susantitaphong P, Cruz DN, Cerda J, et al. Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol*. 2013;8:1482-1493.
4. Dasta JF, Kane-Gill SL, Durtschi AJ, Pathak DS, Kellum JA. Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. *Nephrol Dial Transplant*. 2008;23:1970-1974.
5. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. Cost and mortality associated with postoperative acute kidney injury. *Ann Surg*. 2015;261:1207-1214.
6. Vieira JM Jr, Castro I, Curvello-Neto A, et al. Effect of acute kidney injury on weaning from mechanical ventilation in critically ill patients. *Crit Care Med*. 2007;35:184-191.
7. Selby NM, Kolhe NV, McIntyre CW, et al. Defining the cause of death in hospitalised patients with acute kidney injury. *PLoS One*. 2012;7:e48580.
8. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med*. 2008;359(1):7-20.
9. Uchino S, Bellomo R, Morimatsu H, et al. Continuous renal replacement therapy: a worldwide practice survey. The beginning and ending supportive therapy for the kidney (B.E.S.T. kidney) investigators. *Intensive Care Med*. 2007;33:1563-1570.
10. Siew ED, Davenport A. The growth of acute kidney injury: a rising tide or just closer attention to detail? *Kidney Int*. 2015;87:46-61.
11. Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY. Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol*. 2013;24:37-42.
12. Xue JL, Daniels F, Star RA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J Am Soc Nephrol*. 2006;17:1135-1142.
13. Saran R, Li Y, Robinson B, et al. US Renal Data System 2015 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis*. 2016;67(3 suppl 1):S1-S434.
14. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol*. 2005;16:3365-3370.
15. Fischer MJ, Brimhall BB, Lezotte DC, Glazner JE, Parikh CR. Uncomplicated acute renal failure and hospital resource utilization: a retrospective multicenter analysis. *Am J Kidney Dis*. 2005;46:1049-1057.
16. Kerr M, Bedford M, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in England. *Nephrol Dial Transplant*. 2014;29:1362-1368.
17. De Smedt DM, Elseviers MM, Lins RL, Annemans L. Economic evaluation of different treatment modalities in acute kidney injury. *Nephrol Dial Transplant*. 2012;27:4095-5101.
18. Srisawat N, Lawsin L, Uchino S, Bellomo R, Kellum JA; BEST Kidney Investigators. Cost of acute renal replacement therapy in the intensive care unit: results from The Beginning and Ending Supportive Therapy for the Kidney (BEST Kidney) study. *Crit Care*. 2010;14:R46.
19. Agency for Healthcare Research and Quality. Healthcare Cost and Utilization Project (HCUP). Overview of the National (Nationwide) Inpatient Sample (NIS). Available at: http://www.hcup-us.ahrq.gov/nisoverview.jsp. Accessed January 10, 2016.
20. Lenihan CR, Montez-Rath ME, Mora Mangano CT, Chertow GM, Winkelmayer WC. Trends in acute kidney injury, associated use of dialysis, and mortality after

cardiac surgery, 1999 to 2008. *Ann Thorac Surg*. 2013;95:20-28.
21. Waikar SS, Wald R, Chertow GM, et al. Validity of international classification of diseases, ninth revision, clinical modification codes for acute renal failure. *J Am Soc Nephrol*. 2006;17:1688-1694.
22. Grams ME, Waikar SS, MacMahon B, Whelton S, Ballew SH, Coresh J. Performance and limitations of administrative data in the identification of AKI. *Clin J Am Soc Nephrol*. 2014;9:682-689.
23. Blough DK, Madden CW, Hornbrook MC. Modeling risk using generalized linear models. *J Health Econ*. 1999;18:153-171.
24. Malehi AS, Pourmotahari F, Angali KA. Statistical models for the analysis of skewed healthcare cost data: a simulation study. *Health Econ Rev*. 2015;5:11.
25. Cameron AC, Windmeijer FA. An R-squared measure of goodness of fit for some common nonlinear regression models. *J Econometrics*. 1997(77):329-342.
26. Coca SG. Acute kidney injury in elderly persons. *Am J Kidney Dis*. 2010;56:122-131.
27. Bonventre JV, Basile D, Liu KD, et al; Kidney Research National Dialogue (KRND). AKI: a path forward. *Clin J Am Soc Nephrol*. 2013;8:1606-1608.
28. Okusa MD, Rosner MH, Kellum JA, Ronco C; Acute Dialysis Quality Initiative XIII Workgroup. Therapeutic targets of human AKI: harmonizing human and animal AKI. *J Am Soc Nephrol*. 2016;27:44-48.
29. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M; Alberta Kidney Disease Network. Renal replacement therapy in patients with acute renal failure: a systematic review. JAMA. 2008;299:793-805.
30. Silver SA, Cardinal H, Colwell K, Burger D, Dickhout JG. Acute kidney injury: preclinical innovations, challenges, and opportunities for translation. *Can J Kidney Health Dis*. 2015;2:30.
31. Stewart J, Findlay G, Smith N, Kelly K, Mason M. Adding insult to injury: a review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure). A report by the National Confidential Enquiry into Patient Outcome and Death 2009. Available at: http://www.ncepod.org.uk/2009aki.html. Accessed April 4, 2016.
32. Society of Critical Care Medicine. Surviving Sepsis Campaign. Available at: http://www.survivingsepsis.org /Pages/default.aspx. Accessed April 3, 2016.
33. Mehta RH, Montoye CK, Gallogly M, et al; GAP Steering Committee of the American College of Cardiology. Improving quality of care for acute myocardial infarction: The Guidelines Applied in Practice (GAP) Initiative. *JAMA*. 2002;287:1269-1276.
34. Lewis WR, Peterson ED, Cannon CP, et al. An organized approach to improvement in guideline adherence for acute myocardial infarction: results with the Get With The Guidelines quality improvement program. *Arch Intern Med*. 2008;168:1813-1819.
35. Schwamm LH, Fonarow GC, Reeves MJ, et al. Get With the Guidelines–stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107-115.
36. Maynard G. Preventing Hospital-associated Venous Thromboembolism: A Guide for Effective Quality Improvement. 2nd ed. Rockville, MD: Agency for Healthcare Research and Quality; October 2015. AHRQ Publication No. 16-0001-EF.
37. NHS England: Acute kidney injury programme. Available at: http://www.Thinkkidneys.nhs.uk. Accessed April 3, 2016.

Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery

The Prospective Randomized BigpAK Study

Ivan Göcze, MD, Dominik Jauch, MD,† Markus Götz, MD,* Pascal Kennedy,* Bettina Jung, MD,‡ Florian Zeman,§ Carsten Gnewuch, MD,¶ Bernhard M. Graf, MD,|| Wolfgang Gnann,** Bernhard Banas, MD,‡ Thomas Bein, MD,|| Hans J. Schlitt, MD,* and Tobias Bergler, MD‡*

Objective: To determine the impact of renal biomarker–guided implementation of the Kidney Disease Improving Global Outcomes (KDIGO) care bundle on the incidence of acute kidney injury (AKI) after major noncardiac surgery in a single-center unblinded randomized clinical trial.

Background: Early optimization of volume status and discontinuation of nephrotoxic medication before the occurrence of AKI may be the crucial step to reduce preventable AKI.

Methods: The urinary biomarker–triggered KDIGO care bundle (early optimization of fluid status, maintenance of perfusion pressure, discontinuation of nephrotoxic agents) was compared to standard intensive care unit (ICU) care in 121 patients with an increased AKI risk after major abdominal surgery that was determined by urinary biomarker (inhibitor of metalloproteinase-2 × insulin-like growth factor–binding protein 7) >0.3. Incidence of overall AKI, severity of AKI, length of stay, major kidney events at discharge, and cost effectiveness were evaluated.

Results: The overall stages of AKI were not statistically different between the 2 groups, but in patients with inhibitor of metalloproteinase-2 × insulin-like growth factor–binding protein 7 values of 0.3 to 2.0 a subgroup analysis demonstrated a significantly reduced incidence of AKI 13/48 (27.1%) in the intervention group compared to control 24/50 (48.0%, $P = 0.03$). Incidence of moderate and severe AKI ($P = 0.04$), incidence of creatinine increase >25% of baseline value ($P = 0.01$), length of ICU, and hospital stay ($P = 0.04$) were significantly lower in the intervention group. Intervention was associated with cost reduction. There were no significant differences regarding renal replacement therapy, in-hospital mortality, or major kidney events at hospital discharge.

Conclusions: Early biomarker-based prediction of imminent AKI followed by implementation of KDIGO care bundle reduced AKI severity, postoperative creatinine increase, length of ICU, and hospital stay in patients after major noncardiac surgery.

From the *Department of Surgery, University Hospital Regensburg, Germany; †Department of Surgery, University Hospital Freiburg, Germany; ‡Department of Nephrology, University Hospital Regensburg, Germany; §Center for Clinical Studies, University Hospital Regensburg, Germany; ¶Institute for Clinical Chemistry and Laboratory Medicine, University Hospital Regensburg, Germany; ||Department of Anesthesiology, University Hospital Regensburg, Germany; and **Center for Business Development, University Hospital Regensburg, Germany.

I.G. received lecture fee from Ortho Clinical Diagnostic and Astute Medical. Other authors report no conflicts of interests.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.annalsofsurgery.com).

Reprints: Ivan Göcze, MD, Department of Surgery and Surgical Intensive Care, University Hospital Regensburg, Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany. E-mail: ivan.goecze@ukr.de.

ISSN: 0003-4932/16/XXXX-0001
DOI: 10.1097/SLA.0000000000002485

Keywords: acute kidney injury, biomarker, Kidney Disease Improving Global Outcome recommendation, major surgery

(*Ann Surg* 2017;xx:xxx–xxx)

Acute kidney injury (AKI) is a well-known complication in patients after major surgery.[1–3] Incidence rates of AKI after surgery vary between 13%[4] and 50%,[5] although AKI requiring renal replacement therapy (RRT) is relatively rare (2.3%–6.8%).[6] AKI does not only negatively affect patient morbidity and mortality[7] but also health care costs.[8,9] The impact of AKI requiring renal replacement is reflected by increased mortality rates[4] and poor patient outcome.[10] In contrast to already identified presurgical risk factors for postsurgical AKI, such as hypertension, diabetes mellitus, or preexisting chronic kidney disease,[2,5,3] the consequences of intra- and perioperative AKI management are still under debate. The advantages of conservative fluid administration for perioperative morbidity have been recently emphasized,[11–13] but patients may develop postoperative hypovolemia associated with AKI.[14]

In spite of increasing knowledge about caring for postoperative patients and the pathophysiological mechanisms of AKI, specific treatment options for AKI are limited. In previous studies, interventions were generally started after clinical evidence of changes in kidney function, such as elevated serum creatinine levels or decline in diuresis. However, no adequate therapeutic concepts have yet been established, because such "delayed approaches" may only address already existing kidney damage but not ongoing kidney injury. Therefore, increasing efforts should focus on the early detection and prevention of AKI. Instead of monitoring the traditional surrogate markers of kidney function [serum creatinine, estimated gromerular filtration rate (eGFR), or urine output], newly established biomarkers allow the detection of kidney injury before the manifestation of concurrent or subsequent clinical signs.

The insulin-like growth factor–binding protein 7 (IGFBP7) and the tissue inhibitor of metalloproteinase-2 (TIMP-2) are 2 urinary cell cycle arrest biomarkers used to predict AKI after major cardiac[15] and noncardiac surgery.[16] Both markers are involved in G1 cell cycle arrest that prevents cells from dividing in case of cellular stress.[17] We hypothesized that the biomarker-triggered Kidney Disease Improving Global Outcome (KDIGO) care bundle consisting of early optimization of fluid status, maintenance of perfusion pressure, and discontinuation of nephrotoxic agents may reduce postoperative AKI. To prove the hypothesis, we conducted a single-center randomized trial as a first step before preparing a multicenter randomized study in patients after major noncardiac surgery.

METHODS

Patients and Study Design

For this prospective randomized clinical study intensive care unit (ICU) patients after major elective noncardiac surgery, who were

at risk for AKI, were screened for urine biomarker TIMP-2 × IGFBP7 levels. Patients with levels above the cutoff (>0.3) were randomly allocated to either receive measures of KDIGO care bundle or standard care treatment. The study was conducted in a multidisciplinary surgical ICU of a tertiary care university hospital between May 1, 2015 and December 31, 2016. The study protocol was approved by the local Institutional Review Board (Ethics Committee, University of Regensburg, no. 15-101-0028). Written consent was obtained from eligible patients or from their legally authorized representatives. Deferred consent was used in patients for whom prospective informed consent was not feasible. Furthermore, the responsible ICU physician, who was not involved in the clinical study, had the authorization to withhold an intervention, if medically contraindicated. After recovery, patients had the right to affirm or withdraw their consent. The study is registered at ClinicalTrials.gov, number NCT02500394. Patients eligible for biomarker assessment had to be adults admitted to the ICU after major nonurgent noncardiac surgery (surgery duration of >4 h), who had intraoperatively received a jugular central venous line and a urinary catheter and who had at least 1 additional risk factor for AKI, such as age >75, critical illness, pre-existing chronic kidney disease (eGFR ≤60 mL/min), or intraoperative use of an intravenous radiocontrast agent. Critical illness was defined as ongoing requirement of inotropic support or mechanical ventilation at the time of ICU admission. Exclusion criteria were a preoperative episode of AKI during the same hospital stay, AKI during surgery before biomarker evaluation (because current data suggest a detrimental effect of increased fluid administration in early AKI on renal recovery),[18] pre-existing severe chronic kidney disease (estimated glomerular filtration rate of <15 mL/min), previous RRT or kidney transplantation, pregnancy, breastfeeding, or participation in other interventional trial.

Randomization and Intervention

Eligible patients were screened for increased levels of urinary TIMP-2 × IGFBP7 measured immediately after admission to the ICU and after 12 hours. Using the Astute Medical NephroCheck Test, a point of care unit-use immunofluorescence assay on the ASTUTE140 Meter with a 20-minute reaction time, AKI risk (TIMP-2 × _IGFBP7) was derived from (cTIMP-2 × _cIGFBP7)/1000 with a 0.3 (ng/mL)^2/1000 cut-off. In a preanalytical phase, the precision and accuracy of the test were checked, the SOPs prepared, and the laboratory staff trained for 24-hour test availability. The laboratory personnel processing the biomarker and creatinine assessment had no knowledge of patient allocation. Patients with elevated biomarkers at ICU admission (>0.3) were classified as having a high risk of AKI and were randomized in a ratio of 1:1 to intervention or standard care. Randomization was stratified by TIMP2 × IGFBP7 0.3 to 2.0 and TIMP-2 × IGFBP7 >2.0,[15] and block randomization was used within each stratum. Participants were allocated to the next sequential randomization number by sealed opaque envelopes.

Patients were randomized within 4 hours after ICU admission. The nature of the intervention did not allow masking of the study. Patients of the standard care group received standard ICU therapy that was based on the clinical condition of the individual patient without any information on the elevated biomarker. Standard care included a weekly assessment of the concurrent medication by an ICU pharmacist. We used the same balanced electrolyte infusion in both groups. The initial maintenance rate of continuous infusion was 100 mL/h in both groups. The standard care group received additional fluid infusion as a fluid bolus therapy (FBT) of 500 mL during 30 minutes to 1 hour, if deemed necessary by the responsible physician. Patients in the intervention group received a care bundle according to KDIGO recommendation that consisted of increased continuous intravenous fluid administration for 6 hours in combination with nephrology consultation (Supplemental Digital Content 1, http://links.lww.com/SLA/B318). Fluid administration was guided by central venous pressure (CVP). The algorithm of the fluid therapy was supported by clinical evidence and had a good cardiovascular safety profile.[19] Before the start of fluid intervention, fluid responsiveness was confirmed by one of the following dynamic tests: fluid challenge of 200 mL over 10 minutes, positive leg-raising test, or ultrasound assessment of the inferior vena cava. For patients weighing more than 100 kg, the infusion rate was limited to that calculated for patients weighing 100 kg. An additional fluid bolus of 500 mL was allowed in the intervention group, if deemed necessary by the responsible ICU team. Nephrology consultation conducted by a board-certified nephrologist took place after randomization and before the start of fluid intervention. If necessary, the nephrologist recommended adjustments of the current medication because of potential nephrotoxicity and advised on managing the hemodynamic, acid-base, electrolyte, and albumin status.

Outcomes

The primary endpoint was the incidence of AKI according to the KDIGO 2012 guidelines during the first 7 days after surgery.[20] Secondary outcomes included the incidence of moderate and severe AKI, increase in serum creatinine levels by ΔSCr >25% (because current data have shown a significant impact of small postoperative SCr changes on outcome in surgical patients),[21] hospital and ICU length of stay, the incidence of major kidney events (MAKEs) at discharge (defined as >50% increase in creatinine levels compared to baseline, use of RRT, and in-hospital death), changes in biomarker values during the first 12 hours after admission, subgroups analysis of biomarker strata, measures taken as a consequence of nephrology consultation, and cost-effectiveness analysis. SCr was measured before surgery, at admission to the ICU, on a daily basis during the ICU stay, and as indicated by the responsible physician during the stay at the general ward. Urine output was assessed hourly in the ICU. Cost-benefit analysis was based on specifications of InEK (Institut für das Entgeltsystem im Krankenhaus)—Institute for Payment System in Hospitals. Data for analysis were generate from the Verband der Universitätsklinika Deutschlands benchmark for university hospitals [Regensburg data set, departmental browser (FAB)] and internal occupancy statistics in reference year 2016.

Statistics

Sample Size Calculation

Sample size calculation had been based on the primary endpoint, the incidence of AKI during the first 7 days after surgery. According to our previously published data, we expected an AKI rate of 42% in the standard care group.[16] According to the literature and our clinical experience, we estimated a reduction in AKI to 20% in the intervention group.[19,22] To detect a difference of 42% versus 20% using a chi-square test with a power of 80% ($\beta = 0.2$) at a 5% significance level ($\alpha = 0.05$), a total of n = 138 (n = 69 per group) patients were required. However, as an interim patient analysis (n = 52) indicated that full study recruitment (n = 138) would be unable to detect a statistically significant difference in primary outcome, the study was prematurely terminated on 31st December 2016.

Statistical Analyses

Continuous data are presented as median (first quartile to third quartile) and categorical data as absolute frequencies (%). Baseline characteristics between the 2 study groups were compared with the nonparametric Mann-Whitney *U* test or the chi-square test. The primary endpoint was analyzed using a logistic regression model

with "occurrence of AKI" (yes vs no) as a dependent variable and "study group" as an independent variable. Odds ratio and corresponding 95% confidence interval (CI) are reported as effect estimates. Secondary endpoints (moderate and severe AKI, relevant SCr increase, and MAKE by discharge) were analyzed equivalently to the primary endpoint. ICU and hospital length of stay, biomarkers values, and laboratory variables were compared using the Mann-Whitney *U* test with the Hodges-Lehmann estimator and corresponding exact conditional nonparametric CIs as effect estimates. ICU length of stay was visualized by a Kaplan-Meier plot. A *P* value of <0.05 was considered statistically significant. All analyses were conducted using R version 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

Approximately 43% (N = 102) of 237 screened patients showed normal urine biomarker values and 57% (N = 135) had TIMP2 × IGFBP7 of >0.3. The overall occurrence of AKI was 43.0% (58/135) in the group with elevated TIMP-2 × IGFBP7 levels (>0.3); 37 (27.4%), 14 (10.4%), and 7 (5.2%) were classified as KDIGO stages 1, 2, and 3, respectively.

In total, 125 patients were randomized. However, 2 patients allocated to the intervention group had markedly elevated and not reproducible CVP values, 1 patient was not deemed to be fit by the responsible physician to receive increased maintenance fluid administration because of a substantial risk of developing cardiac insufficiency, and 1 patient allocated to the standard care group required urgent relaparotomy <12 hours after admission. Therefore, 60 patients were included in the intervention group and 61 patients in the standard care group for final assessment (Fig. 1). The baseline characteristics of the study participants were well balanced between the 2 groups (Table 1). The median laboratory turnaround time (from sample registration to results reporting) for urinary (TIMP2 × IGFBP7) was 69 minutes. Time between ICU admission and the start of randomization was 4 hours (median Q1, Q3: 3.0, 5.0). CVP remained stable during the 2 measurements: median of 6.0 mm Hg (Q1, Q3 3.0, 8.0) before intervention and 6.0 mm Hg (4.0, 8.0) after 3 hours. In the intervention group, the median amount of maintenance fluid was 212.5 mL/h (160, 320) at a rate of 3.0 mL/kg/h (2.5, 4.9) in the 0- to 3-hour interval and 200 mL/h (150, 250) at

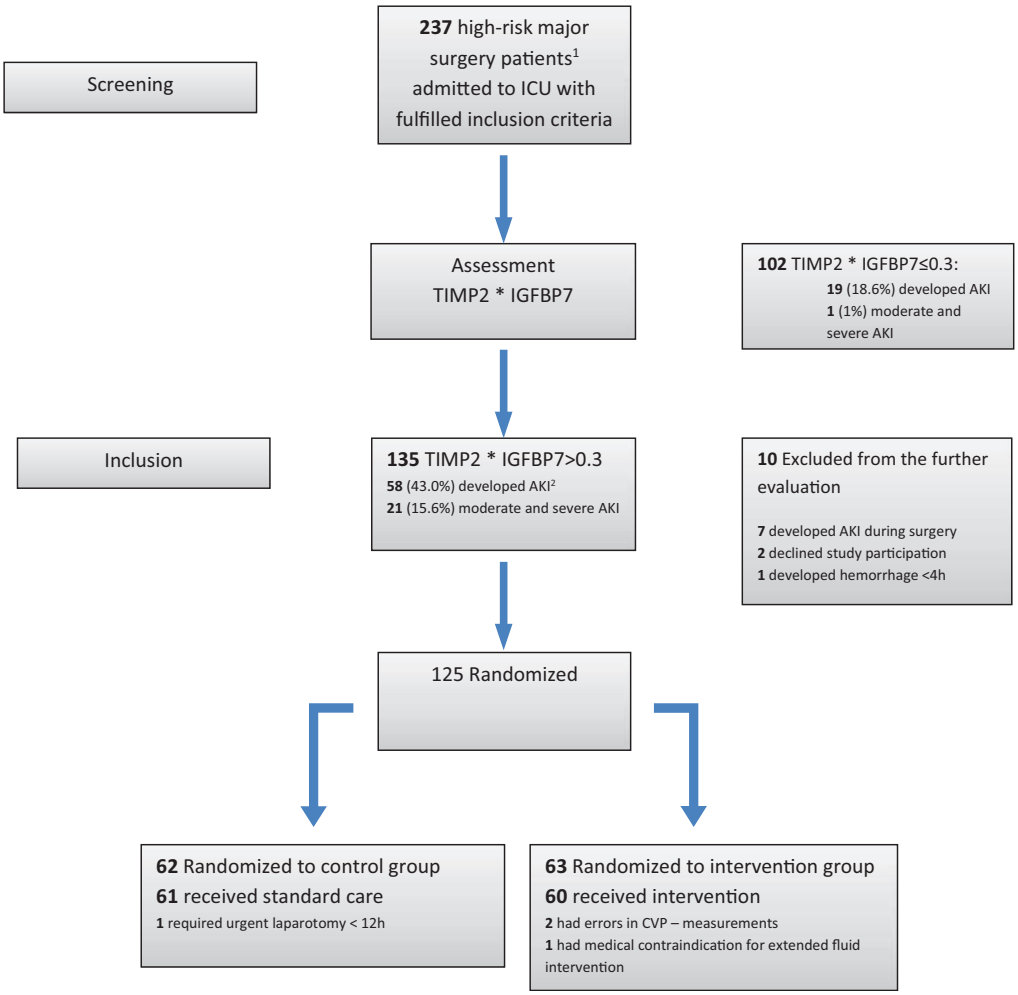


FIGURE 1. Study design and flow diagram. [1]High risk forAKI—elective major surgery >4 hours and 1 additional risk factor: age >75, critical illness, chronic renal disease, or use of radiocontrast agent during surgery. [2]AKI was defined according to KDIGO Criteria 2012.

TABLE 1. Baseline Characteristics for Patients Receiving Intervention Versus Standard Care

	Intervention n = 60	Standard Care n = 61	*P*
Age, median (IQR)	63 (55.25–73)	65 (57.5–74.5)	0.551
Sex (%)			0.957
Male	44 (73.3)	45 (73.8)	
Female	16 (26.7)	16 (26.2)	
BMI, median (IQR)	25.11 (22.66–28.72)	24.86 (23.47–30.03)	0.370
Weight, kg, median (IQR)	78 (64.1–85.75)	80 (69.5–88.7)	0.401
SAPS II, median (IQR)	31 (22–38)	32 (24.5–38)	0.474
Preoperative creatinine, mg/dL, median (IQR)	0.79 (0.69–1.04)	0.83 (0.69–1.00)	0.893
Preoperative GFR (CKD-EPI), mL/min/1.73 qm, median (IQR)	89.5 (69.0–101.0)	88.0 (70.5–98.0)	0.633
Urine output/4 h in mL/kg/h, median (IQR)	0.96 (0.63–1.31)	0.80 (0.55–1.14)	0.291
Baseline urine (TIMP-2) × (IGFBP7), $(ng/mL)^2/1000$, median (IQR)	0.96 (0.70–1.89)	0.86 (0.53–1.62)	0.129
Operative			
Hepatobiliary surgery (%)	22 (36.7)	18 (29.5)	0.405
Transplantation (%)	1 (1.7)	3 (5.0)	0.311
Pancreatic surgery (%)	13 (21.7)	7 (11.5)	0.131
Upper-GI surgery (%)	8 (13.3)	7 (11.5)	0.757
Colorectal surgery (%)	6 (10.0)	13 (21.3)	0.087
Vascular surgery (%)	2 (3.3)	6 (9.8)	0.152
Other abdominal surgery (%)	8 (13.3)	7 (11.5)	0.757
Risk factors			
Age >75 (%)	13 (21.7)	15 (24.6)	0.704
Contrast agent intraoperative (%)	2 (3.3)	6 (9.8)	0.152
Critical illness at admission (%)	56 (93.3)	58 (95.1)	0.682
Chronic kidney disease (%)	8 (13.3)	11 (18.0)	0.477

GI indicates gastrointestinal.

rate of 2.5 mL/kg/h (2.4, 3.1) in the 4- to 6-hour interval. The daily fluid balance for day 1 did not differ between the 2 groups, but on day 2 fluid balance was lower in the intervention group (864 vs 1342 mL), $P = 0.023$. Furthermore, the need for FBT in the first 24 hours was reduced in the intervention compared to the control group [1000 mL (Q1, Q3500, 2000) vs 2000 mL (1000, 2500)], $P < 0.001$. The creatinine values over the first 7 days after surgery and peak creatinine levels did not significantly differ between the 2 groups. However, delta creatinine defined as the ratio between peak SCr and baseline before surgery was lower in the intervention group at day 1 with a median difference of 0.08 (95% CI 0.02, 0.15) and during the 7 days (1.14) (1.05, 1.30) than in the standard care group (1.23) (1.11, 1.43) with a median difference of 0.1 (95% CI 0.02, 0.18), $P = 0.02$. Despite a similar urine output before randomization, this parameter differed between the groups after first 12 hours: 1.35 mL/kg/h (Q1, Q3, 0.94, 1.75) in the intervention group and 1.05 mL (0.84, 1.36) in the standard care group ($P = 0.01$) (Table 2). The postoperative use of albumin and diuretics was similar between the 2 groups.

Primary Endpoint

The overall stages of AKI according to KDIGO classification in the first 7 days after surgery were lower in the intervention group (31.7%) (19/60) than in the standard care group (47.5%) (29/61), $P = 0.076$, odds ratio (OR); 1.96 (95% CI, 0.93, 4.10) without statistical significance. But in patients with TIMP-2 × IGFBP7 values of 0.3 to 2.0 a subgroup analysis demonstrated significant reduced incidence of AKI 13/48 (27.1%) in intervention group compared to 24/50 (48%) in control patients ($P = 0.03$) (Fig. 2).

Secondary Endpoints

Biomarker guided KDIGO care bundle administration significantly reduced the incidence of moderate and severe AKI in the intervention group to 6.7% (4/60 patients) compared to 19.7% in the standard care group (12/60), $P = 0.04$; OR, 3.43 (1.04, 11.32). The incidence of SCr increase by >25% from baseline value was reduced to 40.0% (24/60) in the intervention group versus 62.3% (38/61) in the standard care group, $P = 0.01$; OR, 2.48 (1.19, 5.15). The length of ICU stay was significantly associated with the degree of postoperative change in creatinine levels (Δ creatinine) (Fig. 3). Patients in the intervention group generally had a shorter ICU stay compared to patients receiving standard care, the median difference was 1 (0, 2) day, $P = 0.035$ (Fig. 4). The median length of hospital stay decreased to 16 days[12,22] in the intervention group versus 21 days (15,39) in the standard care group, $P = 0.04$.

Finally, the relative decrease in urinary biomarkers TIMP2 × IGFBP7 values after 12 hours therapy was significantly higher in the intervention group: 2.66 (1.41, 7.04) compared to 1.84 (0.78, 3.19) in the standard care group; the median difference was −0.825 (95% CI −1.7, 0.08], $P = 0.03$. Interestingly, the subgroup analysis suggested significant effect of intervention predominantly in biomarker strata with TIMP2 × IGFBP7 0.3–2.0 (Fig. 2, Fig S1-3, http://links.lww.com/SLA/B318). There were no significant differences in the other secondary outcomes including the use of RRT, in-hospital mortality, as well as MAKE at discharge, although the secondary outcomes trended consistently in favor of intervention (Table 3).

All patients in the intervention group had undergone nephrology consultation before the start of any intervention. Recommendations on current potentially nephrotoxic medications were given for 21 patients (35%). For 6 patients (10%) higher target levels for mean arterial pressure were suggested because of significant pre-existing hypertension. Thirty-two patients (53%) received recommendations for improving acid-base balance, albumin levels, and electrolytes status. Thirteen patients (22%) did not require any nephrology recommendation. The overall-implementation rate of nephrological recommendations was 85% [76% for adjustment of medication (16/21 pts.), 100% for optimization of hemodynamics (6/6 pts.), and 87.5% for achievement of homeostasis (28/32 pts.)]. Reduction of length of ICU stay by 1 day was associated with cost savings of €2031 per patient receiving intervention, taking into account conduction of 2 biomarker tests per patient (Supplemental Digital

TABLE 2. Measures During the Evaluation Period for Intervention Versus Standard Care

	Intervention n = 60	Standard Care n = 61	Effect Estimate* (95%-CI)	*P*
First 12–24 hours after randomization				
Fluid bolus therapy/24 h, mL	1000 (500–2000)	2000 (1000–2500)	500 (500, 1000)	**<0.001**
Albumin dose /24 h, 100 mL	0 (0–1)	1 (0–1)	0 (0, 0)	0.106
Mean MAP/12 h, mm Hg	76.20 (72.18–80.1)	75.40 (70.0–82.30)	−0.55 (−3.2, 2.4)	0.748
Urine output /12 h, mL/kg/h	1.35 (0.94–1.75)	1.05 (0.84–1.36)	−0.25 (−0.46, 0.07)	**0.006**
Urine (TIMP-2) × (IGFBP7) at 12 h, $(ng/mL)^2/1000$	0.40 (0.18–0.95)	0.58 (0.28–1.26)	0.11 (−0.05, 0.28)	0.146
Diuretics dose, mg/48 h	30 (10–50)	30 (10–60)	0 (−10, 10)	0.593
Creatinine values, mg/dL				
Admission to ICU	0.83 (0.70–1.02)	0.85 (0.72–1.08)	0.05 (−0.05, 0.13)	0.336
Day 1	0.86 (0.72–1.05)	0.97 (0.76–1.17)	0.08 (−0.03, 0.19)	0.139
Relative change creatinine day 1 vs baseline	1.07 (0.94–1.17)	1.15 (1.03–1.28)	0.08 (0.02, 0.15)	**0.012**
Day 2	0.82 (0.67–1.13)	0.89 (0.70–1.38)	0.07 (−0.06, 0.2)	0.298
Day 3	0.81 (0.65–1.10)	0.80 (0.64–1.29)	0.03 (−0.09, 0.17)	0.602
Day 4	0.84 (0.63–1.20)	0.89 (0.69–1.46)	0.07 (−0.07, 0.23)	0.293
Day 5	0.76 (0.60–0.92)	0.78 (0.70–1.19)	0.1 (−0.04, 0.24)	0.191
Day 6	0.79 (0.61–1.14)	0.94 (0.69–1.55)	0.12 (−0.06, 0.3)	0.201
Day 7	0.82 (0.65–1.08)	0.83 (0.66–1.17)	0.03 (−0.14, 0.19)	0.812
Peak creatinine	0.92 (0.78–1.28)	0.99 (0.77–1.54)	0.06 (−0.07, 0.19)	0.357
Relative change creatinine peak vs baseline,	1.14 (1.05–1.30)	1.23 (1.11–1.44)	0.1 (0.02, 0.18)	**0.015**
Daily fluid balance on day 1 and day 2, mL				
Fluid intake d1, mL	3714 (3234–4080.5)	3738 (3101.5–4550)	9 (−344, 369)	0.948
Urine output d1, mL	1522.5 (1182.5–1980)	1240 (972.5–1652.5)	−250 (−425, −60)	**0.010**
Daily fluid balance d1, mL	1693.5 (1162.5–2275.8)	1715 (1055–2594)	92 (−313, 469)	0.645
Fluid intake d2, mL	4559 (3748.8–5257.8)	4736 (4123.3–5681.8)	254 (−228, 695)	0.331
Urine output d2, mL	2850 (2407.5–3187.5)	2480 (1975–3105)	−295 (−600, 35)	0.078
Daily fluid balance d2, mL	864 (392–1430)	1342 (730–2199)	405 (61, 764)	0.023*
Cumulative fluid balance d1 + d2, mL	2567 (1617–3706)	3207 (2015.5–4486)	558 (−66, 1196)	0.085

*Hodges-Lehmann estimate (95% CI). All data are presented as median (IQR).

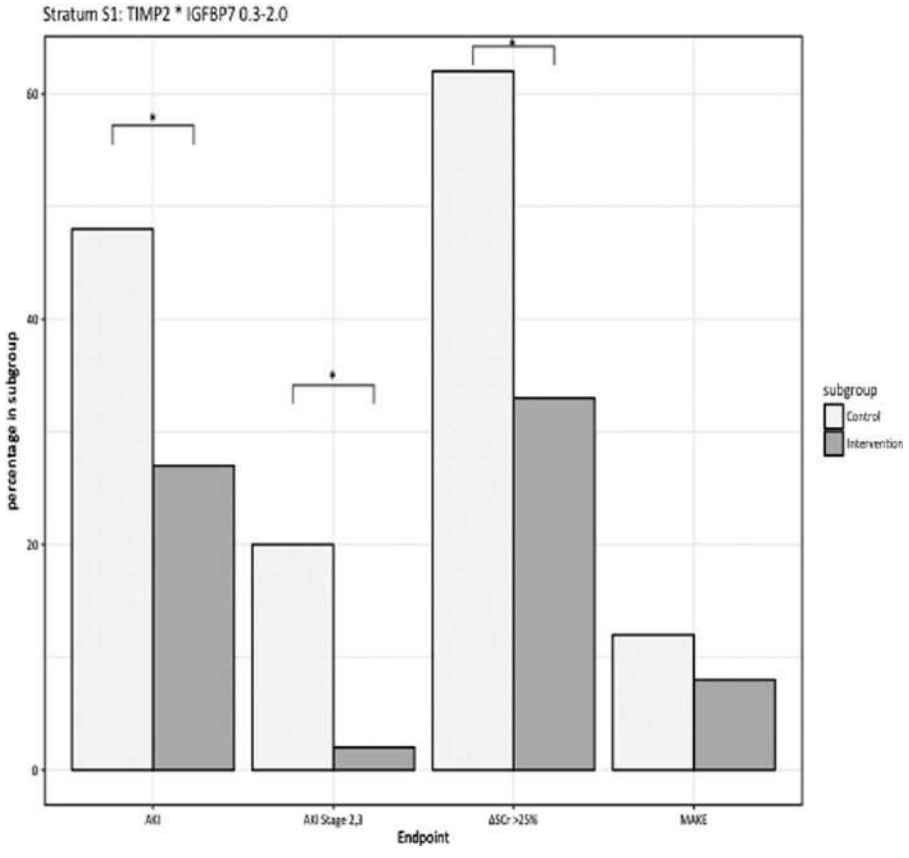


FIGURE 2. Incidence of primary and secondary study endpoints in biomarker stratum TIMP2 × IGFBP7 0.3–2.0 for control (light gray) and intervention (dark gray) group: AKI 24/50 versus 13/48, $P = 0.03$ (Chi-Quadrat test); AKI stage 2,3 10/50 versus 1/48, $P = 0.005$; ΔCr >25% 31/50 versus 16/48, $P = 0.005$; and MAKE 6/50 versus 4/48, P = n.s. Cr indicates creatinine; ΔCr, difference between peak Cr in the first 7 postoperative days and baseline Cr.

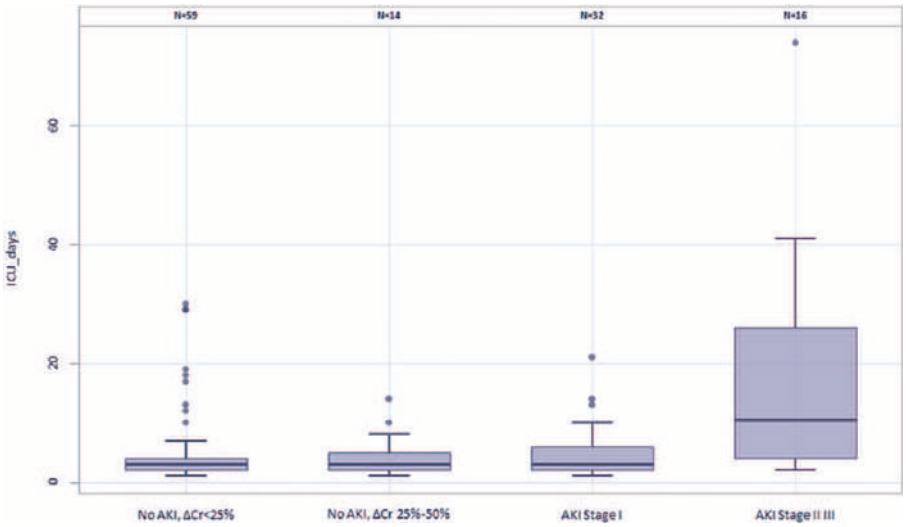


FIGURE 3. Length of ICU stay (medians and percentiles) by severity of acute kidney injury. Length of ICU stay (95% CI) gradually increases the more severe the acute kidney injury (ΔCr <25% vs ΔCr 25%–50% vs. ΔCr 50%–100% vs ΔCr >100%); $P = 0.001$, Kruskal-Wallis test; $P = 0.009$ for No AKI (ΔCR 0–50%) vs AKI (stage I, II, or III) patients (Mann-Whitney *U* test). Cr indicates creatinine; ΔCr, difference between peak Cr in the first 7 postoperative days and baseline Cr.

Content 2, http://links.lww.com/SLA/B318). There was no harm associated with the intervention.

DISCUSSION

In this prospective randomized clinical trial with patients after major noncardiac surgery, early biomarker-triggered implementation of KDIGO care bundle on optimizing volume status in combination with maintenance of adequate perfusion pressure and discontinuation of nephrotoxic agents through nephrology consultation significantly reduced the incidence of moderate and severe AKI. Furthermore postoperative increases in SCr (>25%) and length of stay were reduced. Finally, intervention that can be practiced in every ICU was associated with ICU-costs reduction.

Although a recent meta-analysis reported a pooled AKI incidence of 13.4% in an unselected population of patients after major abdominal surgery,[23] the incidence of all stages AKI in patients with elevated urinary levels (TIMP2 × IGFBP7) in our study was 43%; with 15.6% patients having moderate-severe AKI (equivalent to KDIGO stage 2–3). This effect is consistent with recent findings of the markedly improved detection of high-risk surgical patients for imminent AKI by use of a single urinary (TIMP2 × IGFBP7) test; furthermore, inclusion of such test significantly enhances the performance of clinical risk prediction models.[24]

Once an increased risk of AKI after surgery was detected by means of cell cycle biomarkers in our study, KDIGO care bundle was initiated, always taking into account, that hypervolemia was excluded before and during the intervention. We used the static preload parameter CVP for fluid administration despite the conflicting data on the role of CVP in fluid management. A recent large meta-analysis, however, has reported a reasonable prediction for

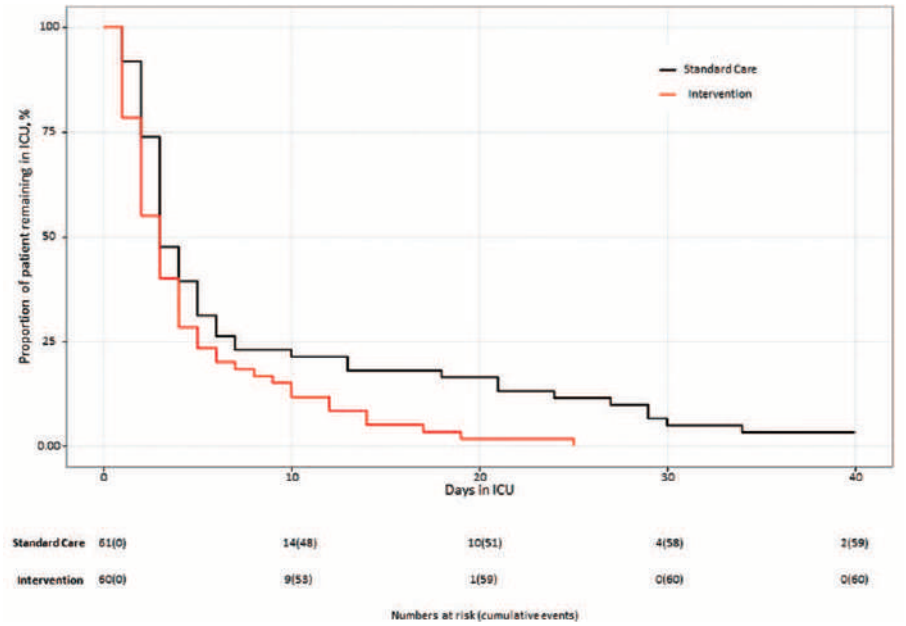


FIGURE 4. Kaplan-Meier plot visualizing patients' days in ICU comparing Standard Care Group and Intervention Group. $P = 0.035$ (Mann-Whitney *U* test). Cr indicates creatinine; ΔCr, difference between peak Cr in the first 7 postoperative days and baseline Cr.

TABLE 3. Clinical Outcomes for Intervention Group Versus Standard Care Group

	Intervention n = 60	Standard Care n = 61	Effect Estimate (95% CI)	*P*
Primary outcome				
Overall AKI (%)	19 (31.7)	29 (47.5)	1.96 (0.93, 4.10)*	0.076
Secondary outcomes				
AKI stage II and III (%)	4 (6.7)	12 (19.7)	3.43 (1.04, 11.32)*	**0.035**
Relevant Cr increase (ΔCr >25%) (%)	24 (40.0)	38 (62.3)	2.48 (1.19, 5.15)*	**0.015**
ICU length of stay, median (IQR) days	3 (2–5)	3 (2–7)	1 (0,2)†	**0.035**
Hospital length of stay, median (IQR) days	16 (12–22)	21 (15–39)	5 (0, 8)†	**0.036**
Requirement of RRT during hospital stay no (%)	2 (3.3)	4 (6.6)	2.04 (0.36, 11.55)*	0.663
In-hospital mortality (%)	4 (6.7)	5 (8.2)	1.25 (0.32, 4.90)*	0.981
MAKE by discharge (%)	5 (8.3)	8 (13.1)	1.66 (0.51, 5.40)*	0.399
Relative change urine (TIMP-2) × (IGFBP7) 12 h vs baseline, $(ng/mL)^2/1000$, median (IQR)	2.66 (1.41–7.04)	1.84 (0.78–3.19)	−0.825 (−1.7, 0.08)†	**0.028**

*Odds ratio (95% CI).
†Hodges-Lehmann estimate (95% CI).

fluid responsiveness with positive predictive values of >60% in range of CVP <6 mm Hg and negative predictive values >60% for CVP >9 mm Hg. These thresholds are very similar to those used in our protocol.[25] Before fluid administration was initiated, fluid responsiveness was tested.[26] In our intervention group, increased maintenance fluid infusion up to 5.0 mL/kg/h for 6 hours was triggered by elevated biomarker values and was given early after admission to the ICU. Interestingly, despite the additional fluid infusion during intervention, the intervention group did not have increased fluid administration. Daily fluid balance for day 1 did not differ between the 2 groups, but fluid balance was lower on day 2. Furthermore, the need for FBT in the first 24 hours was reduced in the intervention group. Although repeated FBT represents the current standard practice of fluid administration, recent studies have indicated only limited hemodynamic effects of such fluid boluses.[27] In a prospective study, an immediate hemodynamic effect on mean arterial pressure and heart rate was seen 10 minutes after FBT. However, these changes were not sustained at 1 and 2 hours after the administration of the fluid bolus. FBT was more commonly associated with adverse effects, such as increased respiratory rate and lower temperature due to the shift in intravascular volume to extravascular space.[28,29] Experimental data on sepsis also showed a greater plasma-expanding effect of slow infusion of albumin during 3 hours versus rapid albumin administration (30 min).[30,31]

We assume that the positive effect of intervention on reducing the incidence and severity of AKI, decrease in postoperative creatinine levels, and length of stay was caused by prediction of imminent AKI at the very early stage followed by ''optimal'' fluid resuscitation with less positive fluid balance and kidney protection. This effect was already present soon after intervention, indicated by significantly improved urine output on day 1, attenuated early (day 1) and total (7 days) increase in creatinine and significant reduction in cellular stress biomarkers (TIMP2 × IGFBP7) over the first 12 hours. Interestingly, effect of intervention on AKI was more pronounced in patients with TIMP2 × IGFBP7 level of 0.3 to 2.0. We hypothesize that the 0.3 to 2.0 range may represent preventable AKI while TIMP2 × IGFBP7 >2.0 is consistent with AKI that is becoming established and can only be managed. However, intervention still may be valuable in these patients since MAKE and length of stay trended downwards with the intervention.

Our study also has some important limitations. The 138 patients included in the calculation were not recruited over the estimated study duration, and this fact can overstate the effect size. The study design as a single-center study of patients after major noncardiac surgery may limit the generalizability of its results. However, a recent study has also shown reduced AKI frequency and severity in cardiac surgery patients after the implementation of KDIGO guidelines. Interestingly, this trial showed a nonsignificant trend toward a higher incidence in adverse kidney events (MAKE, requirement of RRT, and persistent renal dysfunction) in the intervention group.[32] In our study, these outcomes trended consistently in favor of intervention. However, the study was not powered to evaluate these parameters with statistical significance. Clearly, increasing the rate of continuous fluid administration is not suitable for all patients, especially those with high CVP values and negative dynamic test results of fluid responsiveness. Preventive strategies for these patients still need to be evaluated. Finally, this study was not blinded, which could contribute to measurement bias.

In summary, our study provides pilot data that need to be confirmed in an adequately powered multicenter trial. Further studies may also investigate the effect of a biomarker-guided KDIGO care bundle in different surgical subgroups and also address long-term AKI-related outcome parameters.

ACKNOWLEDGMENTS

The authors thank Petra Lehn, MD and Peggy Schwarz for coordination of training, preparation of SOPs, and quality management in implementation of the biomarker analysis in Central Hospital Laboratory.

REFERENCES

1. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. Cost and mortality associated with postoperative acute kidney injury. *Ann Surg*. 2015;261:1207–1214.
2. Long TE, Helgason D, Helgadottir S, et al. Acute kidney injury after abdominal surgery: incidence, risk factors, and outcome. *Anesth Analg*. 2016;122:1912–1920.
3. Yi Q, Li K, Jian Z, et al. Risk factors for acute kidney injury after cardiovascular surgery: evidence from 2,157 cases and 49,777 controls—a meta-analysis. *Cardiorenal Med*. 2016;6:237–250.
4. O'Connor ME, Kirwan CJ, Pearse RM, et al. Incidence and associations of acute kidney injury after major abdominal surgery. *Intensive Care Med*. 2016;42:521–530.
5. Lagny MG, Jouret F, Koch JN, et al. Incidence and outcomes of acute kidney injury after cardiac surgery using either criteria of the RIFLE classification. *BMC Nephrol*. 2015;16:76.
6. Vaara ST, Pettila V, Reinikainen M, et al. Population-based incidence, mortality and quality of life in critically ill patients treated with renal replacement therapy: a nationwide retrospective cohort study in Finnish intensive care units. *Crit Care*. 2012;16:R13.

7. Iwagami M, Yasunaga H, Matsui H, et al. Impact of end-stage renal disease on hospital outcomes among patients admitted to intensive care units: a retrospective matched-pair cohort study. *Nephrology (Carlton)*. 2017;22: 617–623.
8. Dasta JF, Kane-Gill SL, Durtschi AJ, et al. Costs and outcomes of acute kidney injury (AKI) following cardiac surgery. *Nephrol Dial Transplant*. 2008;23: 1970–1974.
9. Gocze I, Bergler T, Bossauer E, et al. The challenge of acute kidney injury: cross-sectional study on prevalence and costs in a university intensive care unit. *Med Klin Intensivmed Notfmed*. 2016;111:501–507.
10. Hobson CE, Yavas S, Segal MS, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. *Circulation*. 2009;119:2444–2453.
11. Glatz T, Kulemann B, Marjanovic G, et al. Postoperative fluid overload is a risk factor for adverse surgical outcome in patients undergoing esophagectomy for esophageal cancer: a retrospective study in 335 patients. *BMC Surg*. 2017;17:6.
12. Healy MA, McCahill LE, Chung M, et al. Intraoperative fluid resuscitation strategies in pancreatectomy: results from 38 hospitals in Michigan. *Ann Surg Oncol*. 2016;23:3047–3055.
13. Schol PB, Terink IM, Lance MD, et al. Liberal or restrictive fluid management during elective surgery: a systematic review and meta-analysis. *J Clin Anesth*. 2016;35:26–39.
14. Schmid S, Kapfer B, Heim M, et al. Algorithm guided goal-directed haemodynamic therapy does not improve renal function after major abdominal surgery compared to good standard clinical care—a prospective randomised trial. *Crit Care*. 2016;20:50.
15. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. *Crit Care*. 2013;17:R25.
16. Gocze I, Koch M, Renner P, et al. Urinary biomarkers TIMP-2 and IGFBP7 early predict acute kidney injury after major surgery. *PLoS One*. 2015; 10:e0120863.
17. Yang QH, Liu DW, Long Y, et al. Acute renal failure during sepsis: potential role of cell cycle regulation. *J Infect*. 2009;58:459–464.
18. Raimundo M, Crichton S, Martin JR, et al. Increased fluid administration after early acute kidney injury is associated with less renal recovery. *Shock*. 2015;44:431–437.
19. Brar SS, Aharonian V, Mansukhani P, et al. Haemodynamic-guided fluid administration for the prevention of contrast-induced acute kidney injury: the POSEIDON randomised controlled trial. *Lancet*. 2014;383:1814–1823.
20. Kellum JA, Lameire N, Aspelin P, et al. KDIGO clinical practice guideline for acute kidney injury 2012. *Kidney Int*. 2012;2:1–138.
21. Kork F, Balzer F, Spies CD, et al. Minor postoperative increases of creatinine are associated with higher mortality and longer hospital length of stay in surgical patients. *Anesthesiology*. 2015;123:1301–1311.
22. Balasubramanian G, Al-Aly Z, Moiz A, et al. Early nephrologist involvement in hospital-acquired acute kidney injury: a pilot study. *Am J Kidney Dis*. 2011;57:228–234.
23. O'Connor ME, Kirvan CJ, Pearse RM, et al. Incidence and associations of acute kidney injury after major abdominal surgery. *Intensive care Med*. 2016;42:521–530.
24. Gunnerson KJ, Shaw AD, Chawla LS, et al. TIMP2.IGFBP7 biomarker panel accurately predicts injury in high risk surgical patients. *J Trauma Acute Care Surg*. 2016;80:243–249.
25. Eskesen TG, Wetterslev M, Perner A. Systematic review including re-analyses of 1148 individual data sets of central venous pressure as a predictor of fluid responsiveness. *Intensive Care Med*. 2016;42:324–332.
26. Cecconi M, De Backer D, Antonelli M, et al. Consensus on circulatory shock and hemodynamic monitoring. Task force of the European Society of Intensive Care Medicine. *Intensive Care Med*. 2014;40:1795–1815.
27. Hoste EA, Maitland K, Brudney CS, et al., ADQI XII Investigators Group. Four phases of intravenous fluid therapy: a conceptual model. *Br J Anaesth*. 2014;113:740–747.
28. Bihari S, Teubner DJ, Prakash S, et al. Fluid bolus therapy in emergency department patients: indications and physiological changes. *Emerg Med Australasia*. 2016;28:531–537.
29. Chowdhury AH, Cox EF, Francis ST, et al. A randomized, controlled, double-blind crossover study on the effects of 2-L infusions of 0.9% saline and plasma-lyte 148 on renal blood flow velocity and renal cortical tissue perfusion in healthy volunteers. *Ann Surg*. 2012;256:18–24.
30. Bark BP, Grände PO. Infusion rate and plasma volume expansion of dextran and albumin in the septic guinea pig. *Acta Anaesthesiol Scand*. 2014;58:44–51.
31. Statkevicius S, Bonnevier J, Bark BP, et al. The importance of albumin infusion rate for plasma volume expansion following major abdominal surgery—AIR: study protocol for a randomised controlled trial. *Trials*. 2016;17:578.
32. Meersch M, Schmidt C, Hoffmeier A, et al. Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial. *Intensive Care Med*. 2017. DOI 10.1007/s00134-016-4670-3.

BIOMÉRIEUX

RISK ASSESSMENT OF ACUTE KIDNEY INJURY USING BIOMARKERS OF KIDNEY STRESS

Selection of publications

2021 EDITION

TIMP-2
IGFBP-7

PIONEERING DIAGNOSTICS

“AKI* occurs in 13.3 million people every year”[1]

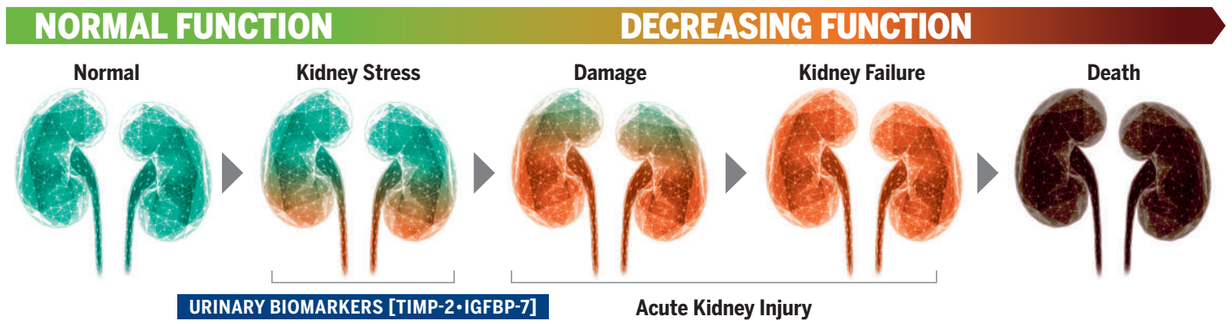
“More than 50% of ICU patients have AKI”[2]

“Hospital mortality rises from 28% to 57% in sepsis patients with AKI”[3]

“23.5% of AKI patients receive RRT – representing a significant healthcare burden”[4]**

Current diagnostic tools are inadequate for assessing the risk of AKI.[5,6]

Urinary biomarkers, [TIMP-2•IGFBP-7]***, are produced during kidney stress and may support earlier intervention before significant kidney injury occurs.[7]



* AKI: Acute Kidney Injury;
** RRT: Renal Replacement Therapy
*** TIMP-2•IGFBP-7: tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein-7

PREFACE

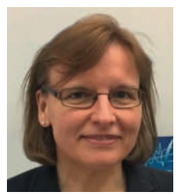
Acute kidney injury (AKI) remains a global challenge affecting about 13.3 million people per year and more than 50% of patients in the intensive care unit (ICU).[8,9] Independent of the etiology, AKI is associated with serious short and long-term complications, including the development of non-renal organ failure, a longer stay in hospital and increased mortality.[10,11] Survivors of AKI are at risk of premature chronic kidney disease (CKD), cardiovascular morbidity, infections, and reduced survival, even if kidney function initially recovers.[12] The risk is highest in patients with more severe AKI, a longer duration of AKI, recurrent episodes and pre-existing CKD. Complete and sustained reversal of AKI within 48–72 hours of the onset is associated with better outcomes than persistent AKI. Not surprisingly, the diagnosis of AKI and long-term kidney disease has a significant impact on well-being and quality of life of patients and their families. Finally, the health care costs for managing AKI exceed those of common cancers.[10,13]

In the absence of a specific therapy for AKI, prevention and mitigation of progression remain high priority to overcome the challenges. For any prevention strategies to be effective, high-risk patients need to be identified before they are exposed to potentially nephrotoxic insults, and **AKI needs to be diagnosed as early as possible**, ideally before any structural damage or functional impairment has occurred. There is increasing evidence that this is possible, thanks to the discovery of new biomarkers which have not only improved our understanding of AKI but also provided opportunities for effective interventions.

The **cell cycle arrest markers tissue inhibitor of metalloproteinases–2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7)** have emerged as effective tools to identify kidney stress before serum creatinine rises or urine output declines.[14] They allow the identification of high-risk surgical patients in whom the application of protocolized goal-directed management can effectively prevent progression to severe AKI.[15-17] Importantly, both positive and negative biomarker results are valuable and may change processes of care and outcomes, especially if combined with traditional investigations and tested repeatedly.[18,19]

For years, serum creatinine has been used to optimize drug dosing despite the fact that creatinine concentrations are influenced by age, sex, race, muscle mass, and dietary intake. Data are accumulating for a refined approach to estimate glomerular function, including the utilisation of new biomarkers.[20]

Based on existing data, a recent international expert committee recommended the **integration of new AKI biomarkers into routine clinical practice**.[21] In particular, it was suggested to combine clinical assessment and validated biomarkers in order to improve the diagnostic accuracy of AKI, to identify different sub-types of AKI, to assess AKI severity and to direct clinical management. At last, there is a prospect of better patient care and improved outcomes.



Marlies OSTERMANN, MD
Consultant in Critical Care & Nephrology,
Guy's & St Thomas' Foundation Trust,
Honorary Senior Lecturer, Kings College,
London, UK

For references, see page 42

CONTENTS

ADDITIONAL RECOMMENDED READING (continued)

International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology.

Mehta RL, Cerdá J, Burdmann EA, et al.
LANCET 2015;385(9987):2616-2643

The impact of biomarkers of acute kidney injury on individual patient care.

Koyner JL, Zarbock A, Basu RK, Ronco C.
NEPHROLOGY DIALYSIS TRANSPLANTATION 2019:1-11. doi:10.1093/ndt/gfz188

Acute Kidney Stress and Prevention of Acute Kidney Injury.

Katz NM, Kellum JA, Ronco C.
CRITICAL CARE MEDICINE 2019;47(7):993-996

Perioperative Acute Kidney Injury: Risk Factors and Predictive Strategies.

Hobson C, Ruchi R, Bihorac A.
CRITICAL CARE CLINICS 2017;33(2):379-396

Cell-cycle arrest and acute kidney injury: the light and the dark sides.

Kellum JA, Chawla LS.
NEPHROLOGY DIALYSIS TRANSPLANTATION 2016;31(1):16-22

EPILAT-IRA Study: A contribution to the understanding of the epidemiology of acute kidney injury in Latin America.

Lombardi R, Ferreiro A, Claure-Del Granado R, et al., EPILAT-ITA Study Group
PLOS ONE 2019;14(11):e0224655

Persistent decrease of renal functional reserve in patients after cardiac surgery-associated acute kidney injury despite clinical recovery.

Husain-Syed F, Ferrari F, Sharma A, et al.
NEPHROLOGY DIALYSIS TRANSPLANTATION 2019;34(2):308-317

Global epidemiology and outcomes of acute kidney injury.

Hoste EAJ, Kellum JA, Selby NM, et al.
NATURE REVIEWS NEPHROLOGY 2018;14(10):607-625.

Financial Impact of Acute Kidney Injury After Cardiac Operations in the United States.

Alshaikh HN, Katz NM, Gani F, et al.
ANNALS OF THORACIC SURGERY 2018;105(2):469-475

ABBREVIATIONS & ACRONYMS

ACE-I	angiotensin-converting-enzyme inhibitor
ADQI	Acute Dialysis Quality Initiative
AIDS	acquired immunodeficiency syndrome
AKI	acute kidney injury
AKI-EPI	Acute Kidney Injury-Epidemiological Prospective Investigation
AKIN	Acute Kidney Injury Network
AKRT	Acute Kidney Response Team
APACHE	Acute Physiology And Chronic Health Evaluation
ARB	angiotensin II receptor blocker
AUC	area under the curve
BUN	blood urea nitrogen
CDSS	Computer Decision Support System
CHF	congestive heart failure
CI	cardiac index
CI	confidence interval
CKD	chronic kidney disease
COPD	chronic obstructive pulmonary disorder
CSA-AKI	cardiac surgery-associated acute kidney injury
CVP	central venous pressure
EMR	electronic medical record
GFR	glomerular filtration rate
HR	heart rate
HVCC	Heart & Vascular Critical Care (Unit)
ICU	Intensive Care Unit
IGFBP	insulin-like growth factor-binding protein
KDIGO	Kidney Disease: Improving Global Outcomes
LOS	length of stay
MAKE	major adverse kidney events
NGAL	neutrophil gelatinase-associated lipocalin
NHS	National Health Service (UK)
NIS	National Inpatient Sample
NSAID	Non-Steroidal Anti-Inflammatory Drug
OR	odds ratio
PAD	pulmonary artery diastolic pressure
PCT	procalcitonin
RCT	randomized controlled trial
RIFLE	Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease
RR	relative risk
RRT	Renal Replacement Therapy
S-AKI	sepsis-associated acute kidney injury
SAPS	Simplified Acute Physiology Score
SBP	systolic blood pressure
SCr	serum creatinine
SOC	standard of care
SOFA	Sequential Organ Failure Assessment
STS	Society of Thoracic Surgeons
SVO2	mixed venous oxygen saturation
TIMP	tissue inhibitor of metalloproteinases
UB	urinary biomarker
UO	urine output

ACUTE KIDNEY INJURY (AKI)

CLICK TO ACCESS ARTICLE

LANCET
2019;394:1949-1964

Acute kidney injury.

Ronco C, Bellomo R, Kellum JA..

Acute kidney injury (AKI) is a syndrome and an important complication that occurs in approximately 10–15% of patients admitted to hospital. In intensive care, its incidence has been reported in more than 50% of patients. Epidemiology studies show that the incidence of AKI is rising, but this is partly due to improved clinical evaluation and detection methods. General risk factors for AKI include advanced age and underlying chronic kidney disease (CKD). AKI rates and causes are found to be highly variable in different countries depending on specific local resources and healthcare systems. The epidemiology of AKI is shown in **Figure 1.**

A major challenge to AKI diagnosis and treatment is that AKI often coexists with other syndromes, such as sepsis, cardiorenal or hepatorenal syndromes. Early and rapid diagnosis and treatment of AKI is therefore an important part of the overall management of patients with such syndromes.

DIAGNOSTIC CRITERIA AND CLINICAL JUDGMENT

Diagnosing AKI requires the clinician to interpret the changes in kidney function in the context of the clinical picture, which is both challenging and complex. International consensus criteria have been developed (ADQI), and later refined (RIFLE, KDIGO) to provide guidance on the diagnosis and staging of AKI, and help standardize the way AKI is reported in clinical trials and epidemiological studies.

CLINICAL COURSE

Nearly two-thirds of AKI cases resolve within 7 days. When a case does not resolve or relapse occurs, substantially worse clinical outcomes are expected. Patients with stage 2–3 AKI who resolve within 7 days and remain free of renal dysfunction by hospital discharge have a 1-year survival of >90%. Patients who do not resolve have a 47% hospital mortality rate and, among those who are discharged, 1-year survival is only 77%. It is therefore important to prevent clinical relapse in patients who have recovered.

DIAGNOSTIC METHODS

When assessing kidney function, changes in serum creatinine (SCr) or urinary output (UO) currently remain the cornerstone of the diagnostic approach, although neither is sensitive or specific for AKI. The discovery of AKI biomarkers and the implementation of computer decision support systems (CDSS) have substantially improved the diagnostic approach to and treatment of AKI. More recently, a second generation of biomarkers has been developed using modern definitions of AKI. Two markers of cell cycle arrest, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) have been incorporated into the first diagnostic test for critically ill patients with AKI approved by the US FDA (NEPHROCHECK®). Such biomarkers of kidney injury or stress are new tools for risk assessment and could possibly guide therapy.

PREVENTION AND MANAGEMENT OF AKI

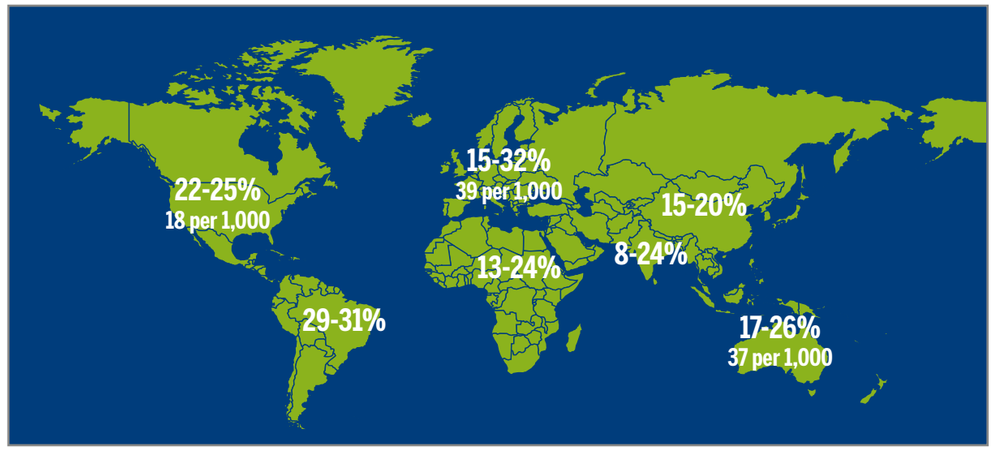
Treating the cause of AKI and avoiding further kidney damage are essential to AKI prevention. Adequate fluid administration and the avoidance of other nephrotoxic drugs are critical. Additionally, the use of urinary biomarkers for early risk assessment to prevent AKI before kidney damage occurs has led to the implementation of specific biomarker-driven care bundles derived from KDIGO recommendations. And a more structured organization of nephrology rapid response teams has contributed to substantially reducing the occurrence of severe AKI cases and the need for Renal Replacement Therapy (RRT).

CONCLUSIONS

The management of patients with AKI has improved alongside improvements in hospital and intensive care quality, supported by more standardized and protocoled management of AKI, the availability of new biomarkers and CDSS, and the demonstrated effectiveness of bundling several interventions on improved patient outcomes.

Near-future challenges include the need for more widespread access to new technologies, and a more sustainable, affordable and effective approach to AKI management in certain geographical areas.

Figure 1. Epidemiology of AKI per hospital admission and corresponding incidence by region
Adapted from Ronco C, et al. *Lancet* 2019;394:1949-1964



"New biomarkers and advanced diagnostic techniques represent an important advancement in the field, leading to implementation of timely and effective preventive and protective measures."

KEY FINDINGS

- AKI occurs in approximately 10–15% of patients admitted to hospital. In intensive care, it has been reported in more than 50% of patients.
- International consensus criteria have been developed for the diagnosis and staging of AKI in order to standardize the way AKI is reported in clinical trials and in epidemiological studies.
- The discovery of new AKI biomarkers, informing clinicians much earlier than historical functional markers (e.g. SCr and UO), and the application of computer decision support systems, have the potential to substantially improve the diagnostic approach to and the treatment of AKI.

CLICK TO ACCESS ARTICLE

INTENSIVE CARE MEDICINE
2015;41:1411–1423

Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study.

Hoste EA, Bagshaw SM, Bellomo R, Cely CM, Colman R, Cruz DN, Edipidis K, Forni LG, Gomersall CD, Govil D, Honoré PM, Joannes-Boyau O, Joannidis M, Korhonen AM, Lavrentieva A, Mehta RL, Palevsky P, Roessler E, Ronco C, Uchino S, Vazquez JA, Vidal Andrade E, Webb S, Kellum JA.

OBJECTIVE

The Acute Kidney Injury-Epidemiological Prospective Investigation (AKI-EPI) was a multicenter international study of the global occurrence and outcomes of AKI in intensive care units (ICUs).

STUDY DESIGN

Investigators at participating ICUs recorded incidence of AKI during the first week of admission in ten or more consecutively admitted ICU patients using a consensus definition of AKI based on the complete KDIGO criteria. A total of 97 ICUs reported on 1,802 patients originating from 33 different countries.

RESULTS

AKI occurred in 57.3% of ICU patients on day one of the ICU stay. KDIGO stage 1 occurred in 18.4% of patients; KDIGO stage 2 in 8.9% and KDIGO stage 3 (the maximum AKI severity) in 30% of patients. Renal Replacement Therapy was used in 13.5% of all patients and 23.5% of patients with AKI during the whole 1-week study period. Increasing AKI severity was associated with increased length of ICU stay, increased length of hospital stay, poorer renal function at time of hospital discharge, and increased mortality.

Comorbidities were present in 71.5% of patients, and 37.6% of patients had two or more comorbidities, such as cancer, hypertension, chronic heart failure, cirrhosis, AIDS, COPD, or diabetes mellitus. Sepsis and hypovolemia were the most frequently reported causes of AKI, followed by nephrotoxic drugs. Hypertension, diabetes, cardiovascular cause of admission, neurosurgery, and SAPS 3 score were all associated with AKI.

CONCLUSIONS

Patients with AKI were older, more often Caucasian, more severely ill, and had worse kidney function at baseline and at the time of ICU admission. After adjustments were made for income, healthcare spending and baseline risk factors, rates of AKI and AKI-related mortality were similar worldwide.

"AKI severity was associated with increased mortality, and this association remained after correction for covariates that may explain mortality. After adjusting for baseline risk there was little variation in AKI occurrence and mortality between different regions in the world."

KEY FINDINGS

- AKI occurred in over half of patients admitted to ICUs.
- Patients who developed AKI had longer lengths of hospital and ICU, and had worse renal outcomes.
- Rates of AKI and mortality for AKI patients were found to be nearly identical between different continents.

CLICK TO ACCESS ARTICLE

BEST PRACTICE & RESEARCH: CLINICAL ANAESTHESIOLOGY
2017;31(3):361-370

Prevention of acute kidney injury.

Meersch M, Volmering S, Zarbock A.

Acute kidney injury (AKI) is a sudden incidence of kidney failure or kidney dysfunction that occurs over several hours or days. It is a reversible condition that can occur in individuals with normal kidney function and in those suffering from chronic kidney disease (CKD). Risk factors include older age, CKD, diabetes, chronic obstructive pulmonary disease, heart failure, sepsis, and shock. Surgical and interventional measures, such as major cardiovascular and abdominal surgery, inotropic support, vasopressors, selective renal ischemia, ischemia-reperfusion injury, administration of nephrotoxic drugs and blood transfusion, have been linked to the development of AKI.

AKI is frequently underdiagnosed, and estimates of incidence vary. Incidence may be as high as 22% in hospitalized patients, and up to 60% in ICU patients. AKI is associated with increased in-hospital mortality, and increased AKI severity is associated with a greater risk of death. Patients who survive an episode of AKI have an almost eight-fold increased risk of CKD and development of end-stage renal disease.

DIAGNOSING AKI

Traditionally, diagnosis and classification of kidney injury severity have been based on serum creatinine levels and urine output over a number of hours. However, these clinical markers are influenced by numerous factors other than renal function, and are lagging indicators of damage. In recent years, new urinary biomarkers have been identified that can detect subclinical AKI during the tubular damage phase prior to functional deterioration. These biomarkers include neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases-2 (TIMP-2), and insulin-like growth factor-binding protein-7 (IGFBP-7). Measurement of the combination biomarker [TIMP-2•IGFBP-7] has recently been recommended to assess risk of AKI in high-risk patients (ICU patients, age >21 years with one further risk factor for AKI, after cardiac bypass or other major high-risk surgery or with sepsis).

AKI GUIDELINES

The KDIGO guidelines recommend supportive measures in high-risk patients: close monitoring of serum creatinine and urine output, optimization in monitoring, discontinuation of nephrotoxic agents, avoidance of hyperglycemia, and remote ischemic preconditioning to reduce AKI. Renal Replacement Therapy (RRT) is currently the only therapeutic choice for treating severe AKI. Early initiation of RRT improves patient outcomes and is associated with a shorter ICU length stay and decreased 28-day mortality.

"A complex multimodal approach including a detailed risk assessment and the implementation of new biomarkers is advisable to prevent and manage AKI."

KEY FINDINGS

- AKI is an underdiagnosed condition that is associated with increased in-hospital morbidity and mortality.
- Use of new biomarkers will provide more rapid detection, risk stratification and earlier intervention in treating AKI in high-risk patients.

CLICK TO ACCESS ARTICLE

KIDNEY INTERNATIONAL
2019;96(5):1083-1099

Acute kidney injury from sepsis: current concepts, epidemiology, pathophysiology, prevention and treatment.

Peerapornratana S, Manrique-Caballero CL, Gomez H, Kellum JA..

Sepsis-associated acute kidney injury (S-AKI) is a common complication of critically ill patients, and is associated with high morbidity and mortality. Prevention of S-AKI is particularly challenging as it is extremely difficult to determine the exact onset of AKI in patients with sepsis, since most patients developing S-AKI will already have AKI on presentation. Early diagnosis and timely intervention are therefore crucial to provide supportive treatment and limit further damage. This review aimed to define the syndrome, determine the role of biomarkers and discuss recent advances in the pathophysiology and treatment of S-AKI.

EPIDEMIOLOGY & PATHOPHYSIOLOGY

Although the global incidence of S-AKI is largely unknown, it is estimated that around 1 in 3 patients with sepsis will develop AKI, and that the annual global incidence might be between 6 and 10 million cases. In the ICU, sepsis is found in about 40%-50% of patients with AKI, and is strongly associated with a poor clinical outcome: higher risk of in-hospital death (odds ratio: 1.48) and longer hospital stay compared with AKI from any other cause (37 vs. 21 days).

Renal replacement therapy (RRT) requirement was strongly associated with hospital mortality, and patients with renal recovery after S-AKI have significantly improved survival rates. Relapse of AKI is common after initial recovery and long-term outcomes of S-AKI patients is determined by AKI severity and recovery status on hospital discharge. S-AKI patients with even partial recovery appear to have a similar prognosis to those without AKI, whereas patients who do not recover have a worse prognosis (44% mortality in moderate to severe S-AKI cases). AKI severity, RRT requirement and recovery status during hospitalization have been shown to be the three key determinants in the risk of progression to chronic kidney disease (CKD).

Although the principal pathophysiologic model currently attributes S-AKI to decreased global renal blood flow and secondary tubular epithelial cell death, or acute tubular necrosis, it is becoming increasingly clear that multiple mechanisms are involved. Recent evidence shows that 3 fundamental mechanisms may play a role in the development of S-AKI: microvascular dysfunction, inflammation, and metabolic reprogramming.

Metabolic reprogramming involves reprioritizing energy to meet vital metabolic needs by maintaining survival at the expense of cell function **(Figure 1)**. For example, during the cell cycle, if the cell does not have sufficient energy to replicate, it will undergo cell cycle arrest to avoid cell death. Cell cycle arrest is therefore one of the mechanisms used in metabolic reprogramming to defend the body against sepsis.

ROLE OF BIOMARKERS

Novel biomarkers of kidney stress and damage have been recently validated for risk prediction and early diagnosis of S-AKI **(Figure 2)**. Urinary tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) are two proteins involved in cell cycle arrest. These urinary biomarkers have been shown to outperform other biomarkers for prediction of AKI with an area under the curve (AUC) of 0.80 (Kashani et al., *Critical Care*, 2013;17(1):R25 - see study summary page 16). Furthermore, unlike many biomarkers, [TIMP-2•IGFBP-7] levels did not increase in non-renal organ failures in sepsis.

PREVENTION AND TREATMENT

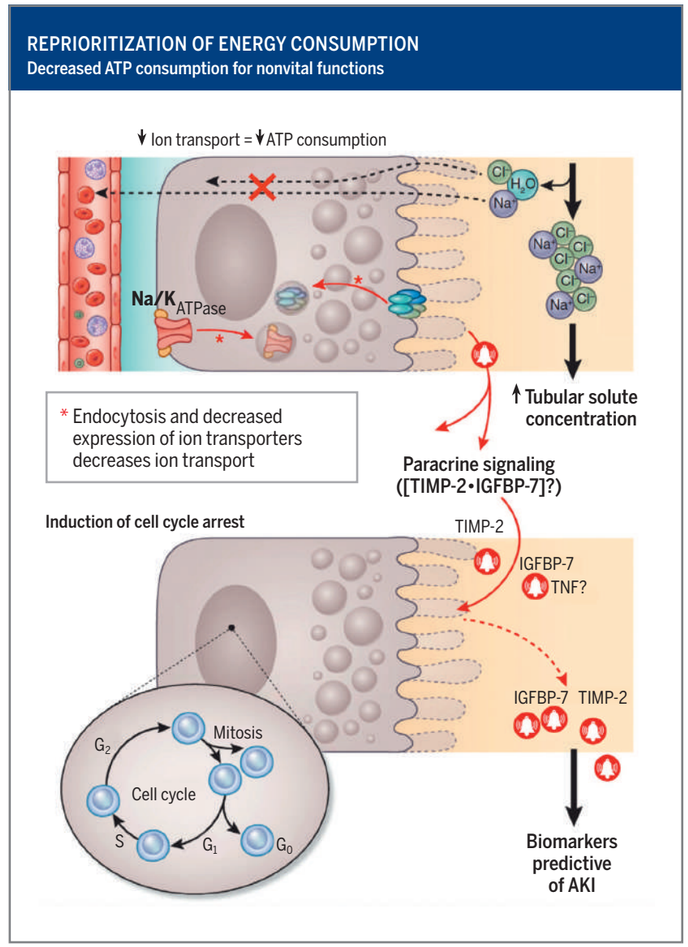
As most patients developing S-AKI will already have it at presentation, AKI is most often impossible to prevent. Early recognition of AKI in the setting of sepsis is therefore vital to provide optimal treatment and avoid further kidney injury. Early appropriate antibiotic administration, fluid resuscitation and source control are the staples of sepsis treatment, and may also prevent further kidney injury. Several new drugs for AKI are currently being investigated, but only a few are focused specifically on S-AKI.

The survival advantage for early initiation of RRT in patients with severe AKI is debatable. Although some studies have shown that early initiation of RRT may result in a significantly reduced rate of major adverse kidney events, mortality, and enhanced renal recovery at 1-year follow-up, further studies are need to provide more conclusive evidence.

CONCLUSIONS

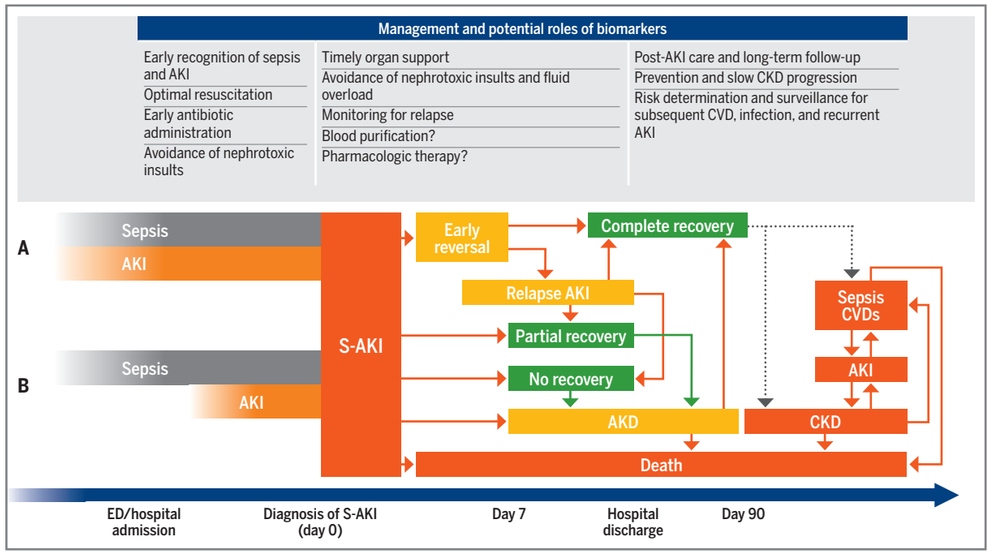
Further research is needed to achieve greater understanding of the underlying mechanisms of S-AKI, as well as more effective interventions for its prevention and treatment. The value of biomarkers to improve early detection of S-AKI has been established as complementary to clinical judgment and functional tests, and can potentially guide patient management and monitor recovery.

Figure 1. Metabolic reprogramming during S-AKI, with reprioritization of energy consumption
Adapted from Peerapornratana S, et al. *Kidney International* 2019;96(5):1083-1099



ATP: adenosine triphosphate; G0–G2: phases of the cell cycle; IGFBP-7: insulin-like growth factor-binding protein-7; TIMP-2: tissue inhibitor of metalloproteinases-2; TNF: tumor necrosis factor

Figure 2. Clinical course and outcomes of S-AKI, with management and potential roles of biomarkers
Adapted from Peerapornratana S, et al. *Kidney International* 2019;96(5):1083-1099



AKI: acute kidney injury; AKD: acute kidney disease; CKD: chronic kidney disease; CVD: cardiovascular disease; S-AKI: sepsis-associated acute kidney injury; ED: emergency department

The exact onset of AKI in sepsis is not well elucidated. AKI may present simultaneously with sepsis at hospital admission **(A)** or develop during hospitalization **(B)**. Novel biomarkers have a place in the early risk assessment of S-AKI, and can guide resuscitation which ultimately can prevent the adverse outcomes associated with S-AKI. Those adverse outcomes include; increased hospital mortality, and post discharge complications such as development of AKD which can subsequently lead to CKD. These post-discharge complications may still arise in patients who have been discharged in seemingly good health, highlighting the need for more intense monitoring and avoidance of renal insults even after early reversal from S-AKI.

"Importantly unlike many biomarkers, non-renal organ failures in sepsis did not result in increased [TIMP-2•IGFBP-7]."

KEY FINDINGS

- S-AKI is a common complication in ICU patients with high morbidity and mortality. Early detection is essential for appropriate patient management and to prevent further organ damage.
- The pathophysiology of this syndrome is complex and a better understanding of the multiple mechanisms causing S-AKI is needed.
- Novel biomarkers of kidney stress, including urinary biomarkers [TIMP-2•IGFBP-7], have been recently validated for risk prediction and early diagnosis of S-AKI.

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

CLICK TO ACCESS ARTICLE

CRITICAL CARE
2013;17(1):R25

Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury.

Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw SM, Bell M, Bihorac A, Birkhahn R, Cely CM, Chawla LS, Davison DL, Feldkamp T, Forni LG, Gong MN, Gunnerson KJ, Haase M, Hackett J, Honore PM, Hoste EA, Joannes-Boyau O, Joannidis M, Kim P, Koyner JL, Laskowitz DT, Lissauer ME, Marx G, McCullough PA, Mullaney S, Ostermann M, Rimmelé T, Shapiro NI, Shaw AD, Shi J, Sprague AM, Vincent JL, Vinsonneau C, Wagner L, Walker MG, Wilkerson RG, Zacharowski K, Kellum JA.

OBJECTIVE

Two multicenter observational studies (discovery and validation) were performed in critically ill patients at risk for acute kidney injury (AKI). The objective was to identify and validate novel biomarkers of AKI.

STUDY DESIGN

In the discovery phase, 522 adult patients with sepsis, shock, major surgery, and trauma were enrolled at three sites. Blood and urine samples from these patients were used to identify the best biomarkers among 340 proteins, some previously characterized and some novel. Biomarkers were ranked by their ability to predict AKI RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) stage within 12-36 hours.

The top two markers from the discovery study were then validated in a second study (Sapphire) and compared to a number of previously described biomarkers. In the validation study, 744 adult subjects were enrolled with critical illness and without evidence of AKI at enrollment; the final analysis cohort was a heterogeneous sample of 728 critically ill patients. The primary endpoint was moderate to severe AKI (KDIGO stage 2 to 3) within 12 hours of sample collection.

RESULTS

Among all permutations of biomarkers tested, the combination of urine insulin-like growth factor-binding protein-7 (IGFBP-7) and tissue inhibitor of metalloproteinases-2 (TIMP-2) best distinguished patients who developed moderate to severe AKI within 12 hours from those who did not. [TIMP-2•IGFBP-7] exhibited an area under the curve (AUC) of 0.80, outperforming all other markers **(Figure 1)**. Both biomarkers are inducers of G1 cell cycle arrest, a key mechanism implicated in the pathogenesis of AKI.

The risk of AKI increased sharply above [TIMP-2•IGFBP-7] 0.3 **(Figure 2)**. When biomarker values were divided into tertiles, the middle tertile had a 3-fold greater risk of AKI and the highest tertile had a nearly 10-fold risk ($p<0.001$) as compared to patients with the lowest tertile values. Further, these biomarkers improved risk prediction when added to a 9-parameter clinical risk assessment model.

CONCLUSIONS

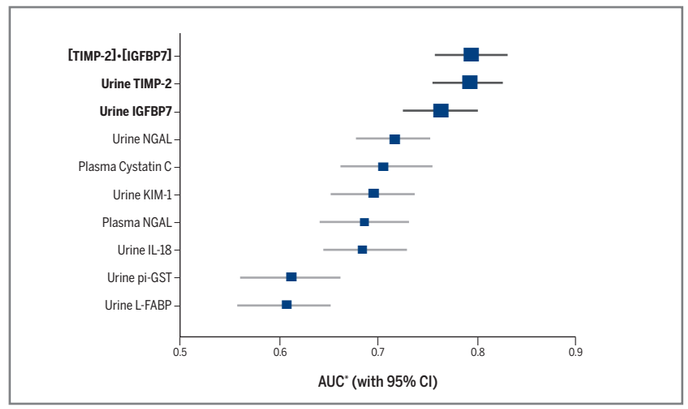
[TIMP-2•IGFBP-7] has been validated in independent multicenter cohorts as a novel biomarker for AKI. The combination biomarker has been shown to be superior to existing markers, providing additional information over clinical variables and a greater understanding of the mechanisms involved in the development of AKI.

"... this new test should significantly improve the ability of physicians caring for critically ill patients to identify risk of impending AKI."

KEY FINDINGS

- [TIMP-2•IGFBP-7] is shown to be a superior combination biomarker for assessing acute kidney stress compared to other candidate biomarkers for AKI.
- [TIMP-2•IGFBP-7] demonstrates specificity to AKI and are not elevated with other acute or chronic conditions.
- [TIMP-2•IGFBP-7] shows a quantitative relationship between the test result and level of risk for AKI.

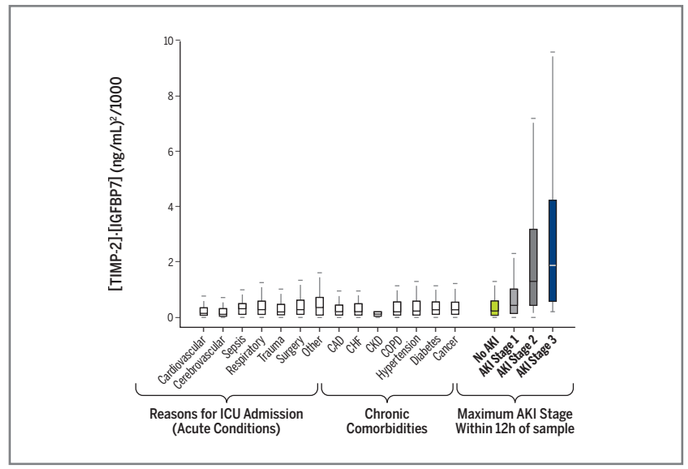
Figure 1. Comparison of Areas under the ROC curve (AUCs) for novel urinary biomarkers and existing biomarkers of AKI for the primary Sapphire study endpoint (KDIGO stage 2 or 3 within 12 hours of sample collection)
Adapted from Kashani et al. *Critical Care* 2013;17(1):R25



*The AUC is a single measure of diagnostic test accuracy that combines sensitivity and specificity.

CI: confidence interval; IGFBP-7: insulin-like growth factor-binding protein-7; IL-18: interleukin-18; KIM-1: kidney injury marker-1; L-FABP: liver fatty acid-binding protein; NGAL: neutrophil gelatinase-associated lipocalin; pi-GST: pi-Glutathione S-transferase; TIMP-2: tissue inhibitor of metalloproteinases-2

Figure 2. Discrimination between non-AKI conditions and AKI of different severities for urine [TIMP-2•IGFBP-7]
Adapted from Kashani et al. *Critical Care* 2013;17(1):R25



CI: confidence interval; IGFBP-7: insulin-like growth factor-binding protein-7; IL-18: interleukin-18; KIM-1: kidney injury marker-1; L-FABP: liver fatty acid-binding protein; NGAL: neutrophil gelatinase-associated lipocalin; pi-GST: pi-Glutathione S-transferase; TIMP-2: tissue inhibitor of metalloproteinases-2

CLICK TO ACCESS ARTICLE

CRITICAL CARE
2019;23(1):225. DOI: 10.1186/S13054-019-2504-8

Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel.

Guzzi LM, Bergler T, Binnall B, Engelman DT, Forni L, Germain MJ, Gluck E, Göcze I, Joannidis M, Koyner JL, Reddy VS, Rimmelé T, Ronco C, Textoris J, Zarbock A, Kellum JA.

OBJECTIVE

A working group of clinical experts convened meetings to discuss their collective experience with the practicalities of implementing the NEPHROCHECK® test, a combination biomarker of tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein (IGFBP-7), known as [TIMP-2•IGFBP-7]. The work group sought to understand how the biomarker test was being used at sites that have adopted it.

STUDY DESIGN

Experts in critical care, nephrology, and surgery who had significant clinical experience with the biomarker were invited to 2 meetings conducted in 2018. One meeting was held in the US and another in the EU.

Prior to the meetings, invitees completed a questionnaire on [TIMP-2•IGFBP-7] testing at their sites. Participants were also encouraged to provide their individual institution protocols and/or written instructions they had developed or with which they were familiar. These protocols were analyzed for common elements, and then rank-ordered by all participants.

RESULTS

Clinical experts from Europe and North America agreed on target testing populations, how to interpret a quantitative test result, and what actions to take based on test results, but achieved less of a consensus on timing of testing. Priority patient populations for measuring kidney stress were patients undergoing major surgery (both cardiac and non-cardiac), patients with hemodynamic instability or with sepsis. Among patients whose values indicated moderate to high risk of AKI, clinicians identified the highest priority actions to be 1) discontinue all nonessential potential nephrotoxins; 2) avoid vancomycin alone or in combination or dose adjust; 3) perform goal-directed fluid management; and 4) discontinue angiotensin-converting-enzyme inhibitors (ACEs) and angiotensin II receptor blockers (ARBs).

CONCLUSIONS

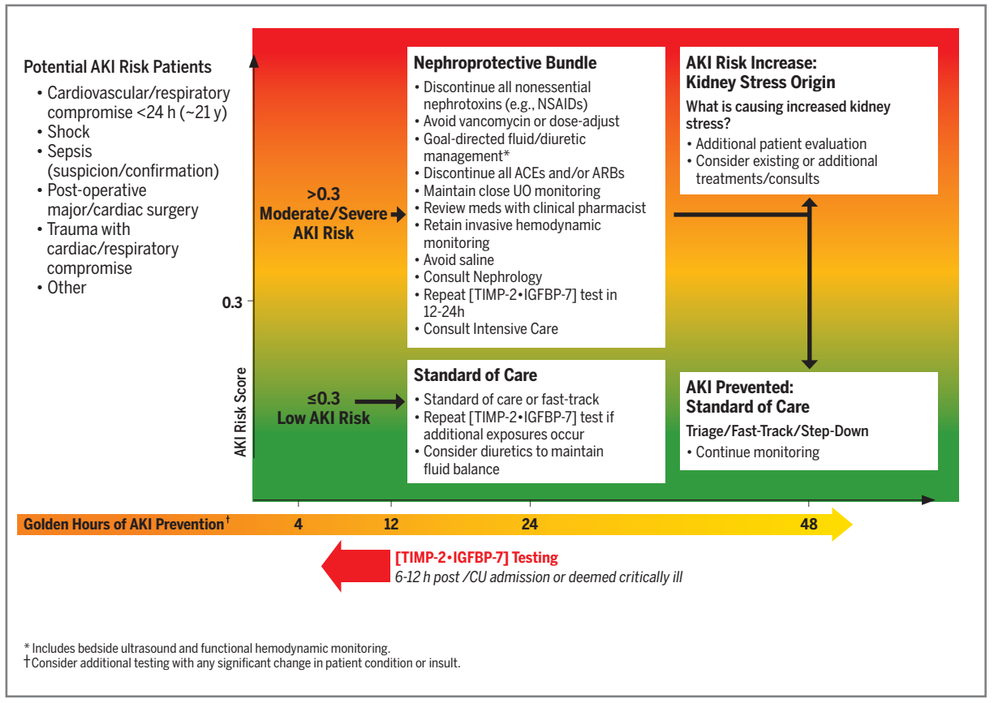
Clinicians reported ordering the NEPHROCHECK test when there was concern that the kidneys were under threat for any reason and there was agreement that testing is especially useful within the first 72 hours of ICU admission. Those patients who tested negative were considered to be excellent candidates for "fast-track" protocols and rapid de-escalation of monitoring.

"By instituting an AKI biomarker protocol, hospitals have the opportunity to develop and test metrics that can enhance quality improvement initiatives."

KEY FINDINGS

- Types of patients being tested and the types of recommended interventions based on the test result were similar. More variation was seen in terms of when to test.
- A negative test result was also considered informative as patients could benefit from treatments best avoided in high-risk patients and monitoring could be de-escalated more rapidly.

Figure 1. Protocol for [TIMP-2•IGFBP-7] testing
Adapted from Guzzi LM, et al. *Critical Care* 2019;23(1):225. doi:10.1186/s13054-019-2504-8



* Includes bedside ultrasound and functional hemodynamic monitoring.
†Consider additional testing with any significant change in patient condition or insult.

CLICK TO ACCESS ARTICLE

CARDIORENAL MEDICINE
2019;9(6):358-369

Serial Urinary Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 and the Prognosis for Acute Kidney Injury over the Course of Critical Illness.

McCullough PA, Ostermann M, Forni LG, Bihorac A, Koyner JL, Chawla LS, Shi J, Kampf JP, McPherson P, Kellum JA.

OBJECTIVE

This is a secondary analysis of data from the previously published Sapphire trial – the prospective, blinded, observational, international study of patients admitted to intensive care units - which demonstrated that initial urine [TIMP-2•IGFBP-7] predicted stage 2/3 AKI within 12 hours and before a rise in serum creatinine (see pages 16-17).This analysis was done to evaluate the utility of serial measurements of [TIMP-2•IGFBP-7] to anticipate the occurrence of AKI over the first 7 days of critical illness.

STUDY DESIGN

Urine samples from 530 patients collected every 12 hours up to 3 days were analyzed. The first 3 measurements (baseline, 12 and 24 hours) were evaluated and if any of these results were >0.3 (ng/mL)²/1,000, additional results were evaluated. Patient stratification was done based on number of results >0.3 (ng/mL)²/1,000 and number of results >2.0 (ng/mL)²/1,000. The primary endpoint was stage 2/3 AKI defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

RESULTS

This analysis demonstrated that serial urinary [TIMP-2•IGFBP-7] at baseline, 12, 24 hours, and up through 3 days are prognostic for the occurrence of stage 2/3 AKI over the course of critical illness **(Figures 1, 2, 3)**.

For patients testing negative <0.3 (ng/mL)²/1,000 for the first 3 tests, the incidence of de novo KDIGO stage 2/3 AKI at 7 days was 13.0%. However, for those with one, two, or three strongly positive values >2.0 (ng/mL)²/1,000, the incidence of stage 2/3 AKI at 7 days was 57.7, 75.0, and 94.4%, respectively (p<0.001 for trend).

CONCLUSIONS

Critically ill patients have frequent and ongoing exposures that can cause AKI. Thus, serum creatinine and blood-urea-nitrogen (BUN) are usually measured daily. This analysis was done to mimic a clinician-driven serial testing strategy. Persistently negative results <0.3 (ng/mL)²/1,000 are associated with very low incidence of stage 2/3 AKI while persistently positive or strongly positive results >2.0 (ng/mL)²/1,000 are associated with progressively higher stage 2/3 AKI rates.

This study was the first to assess serial measurements of [TIMP-2•IGFBP-7] in a large multicenter international cohort of heterogeneous critically ill patients.

"Our results show that sequential measurement of [TIMP-2•IGFBP-7] can complement the information given by serum creatinine in the anticipation of subsequent stage 2/3 AKI."

KEY FINDINGS

- Serial measurement of urine [TIMP-2•IGFBP-7] in critically ill patients every 12 hours for at least 3 samples provided an approach to predict the progressive risk of stage 2/3 AKI up to 7 days in the ICU.
- Three consecutive negative values <0.3 (ng/mL)²/1,000 are associated with very low (13.0%) incidence of stage 2/3 AKI over the course of 7 days.
- Emerging or persistent, strongly positive results >2.0 (ng/mL)²/1,000 predict very high incidence rates (up to 94.4%) of stage 2/3 AKI.

Figure 1. Cumulative incidence of stage 2/3 AKI over 1 week for patients stratified by number of consecutive [TIMP-2•IGFBP-7] above the 0.3 (a) and 2.0 (ng/mL)²/1,000 (b) cutoffs
Adapted from McCullough PA, et al. *Cardiorenal Medicine* 2019;9(6):358-369

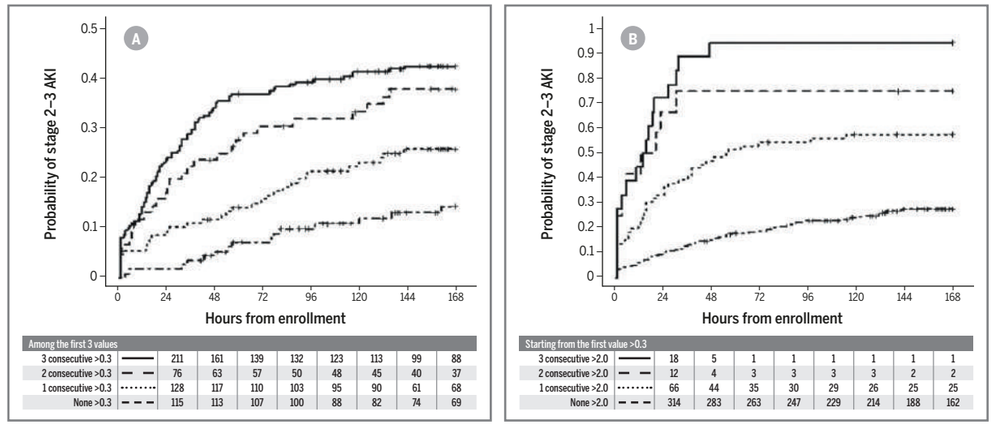


Figure 2. Incidence of stage 2/3 AKI within 1 week of enrollment by number of [TIMP-2•IGFBP-7] values ≤0.3 (a) and >2.0 (ng/mL)²/1,000 (b) among the first 7 measurements collected approximately 12 h apart
Adapted from McCullough PA, et al. *Cardiorenal Medicine* 2019;9(6):358-369

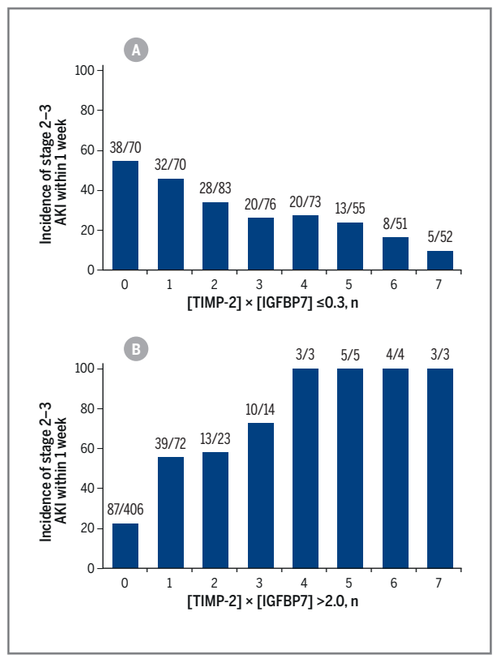
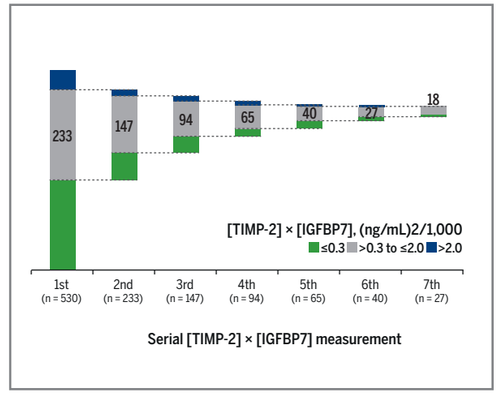


Figure 3. Evolution of patients with [TIMP-2•IGFBP-7] values >0.3 to ≤2.0 (ng/mL)²/1,000 over the first 7 consecutive [TIMP-2•IGFBP-7] measurements collected approximately 12 h apart
Adapted from McCullough PA, et al. *Cardiorenal Medicine* 2019;9(6):358-369



Box shadings show number of patients who started within each [TIMP-2•IGFBP-7] level (1st column) or decreased to ≤0.3 (ng/mL)²/1,000 (gray), remained at >0.3 to ≤2.0 (ng/mL)²/1,000 (white), or increased to >2.0 (ng/mL)²/1,000 (black).

CLICK TO ACCESS ARTICLE

ANNALS OF INTENSIVE CARE
2020;10:46

Urinary [TIMP-2] × [IGFBP7] and serum procalcitonin to predict and assess the risk for short-term outcomes in septic and non-septic critically ill patients.

Godi I, De Rosa S, Martino F, Bazzano S, Martin M, Boni E, Carta MR, Tamayo Diaz C, Mari G, Lorenzin A, de Cal M, Corradi V, Caprara C, Giavarina D, Ronco C.

OBJECTIVE

This study assessed the combination of biomarkers [TIMP-2•IGFBP-7] and procalcitonin (PCT) for AKI prediction and risk stratification in ICU patients. The hypothesis was that the addition of an AKI biomarker with a sepsis biomarker may lead to early identification of patients with sepsis-induced AKI, and measurement of [TIMP-2•IGFBP-7] and PCT on admission may help assess risk of short-term adverse renal outcomes in septic and non-septic patients.

STUDY DESIGN

This retrospective cohort analysis included critically ill adult patients admitted to a multidisciplinary ICU from June 2016–February 2018 and who received [TIMP-2•IGFBP-7] and PCT measurements on ICU admission.

The primary endpoint assessed [TIMP-2•IGFBP-7] and PCT measurements, alone and combined, on ability to predict AKI development within 48 hours. The secondary endpoint assessed the utility of combining results from both biomarkers for risk assessment of AKI within 48 hours, and acute kidney disease (AKD) and mortality at 7 days. To evaluate the utility of combining [TIMP-2•IGFBP-7] and PCT results for risk assessment, the predictive value for single-biomarker positivity was compared to double-biomarker positivity using cut-offs of 0.3 (ng/mL)²/1000 for [TIMP-2•IGFBP-7] and 0.5 µg/L for PCT.

Primary and secondary endpoints were studied in both septic and non-septic patient groups.

RESULTS

Four hundred and thirty-three (433) patients were included in the study, of whom 168 (38.8%) developed AKI within 48 hours (93 septic and 65 non-septic patients).

The combination of [TIMP-2•IGFBP-7] and PCT showed a good predictive ability to predict AKI occurrence (AUC[1] 0.81, 95% CI 0.77–0.86, $p<0.001$, Sensitivity 78%, Specificity 73%).

The presence of at least one of the two biomarkers was significantly associated with AKI development (OR[2] 4.1, 95% CI 1.9–8.8, $p<0.001$) – a 4-fold risk increase for single-marker positivity **(Table 1)**. When both biomarkers were positive, the risk of AKI occurrence increased 26-fold (OR 26.4, 95% CI 12.3–56.62, $p<0.001$).

CONCLUSIONS

The combination of biomarkers showed good predictive ability for patients at risk of developing AKI. The combined results enabled risk stratification for AKI development within 48 hours. The double-marker positivity was significantly associated with mortality within 7 days in the septic subgroup and with AKD at 7 days in non-septic patients **(Table 2)**. Data should be confirmed in a larger prospective study.

[1] AUC: Area Under the Curve; [2] OR: Odds Ratio

"Combining the results of [TIMP-2•IGFBP-7] and PCT may be a useful tool to identify and stratify ICU patients at high risk for septic AKI and short-term adverse outcomes."

KEY FINDINGS

- Combining [TIMP-2•IGFBP-7] and PCT with cut-offs of 0.3 and 0.5 respectively, may help in stratifying ICU patients at high risk of developing AKI (regardless of sepsis).
- The positivity of the two biomarkers showed a 26-fold odds of AKI development, compared with a 4-fold risk increase with only single-marker positivity.
- The double-marker positivity also indicated an elevated risk for AKD at 7 days in non-septic patients and for mortality within 7 days in patients with suspected or confirmed sepsis.

Table 1. Risk assessment for primary and secondary outcomes in the entire population and in septic and non-septic subgroups
Adapted from Godi I, et al. *Annals of Intensive Care* 2020;10:46

Variables	Analysis cohort			Sepsis			Non-sepsis		
	OR	95% CI	*p*-value	OR	95% CI	*p*-value	OR	95% CI	*p*-value
Primary outcome									
AKI within 48 h									
[TIMP-2•IGFBP-7] > 0.3	3.93[a]	2.14–7.20	< 0.001	5.92[a]	2.53–13.82	< 0.001	3.27[a]	1.53–6.97	< 0.001
PCT > 0.5	3.67[a]	2.17–6.19	< 0.001	2.74[a]	0.87–8.57	0.083	4.85[a]	2.37–9.94	< 0.001
Single-marker positivity	4.08	1.90–8.76	< 0.001	2.27	0.45–11.23	0.316	4.93	2.05–11.82	< 0.001
Double-marker positivity	26.41	12.32–56.62	< 0.001	19.5	4.20–90.44	< 0.001	25.11	9.58–65.79	< 0.001
Secondary outcomes									
AKD at 7 days									
Single-marker positivity	4.73	1.04–21.60	0.045	2.28	0.26–20.02	0.15	3.24	0.65–16.20	0.151
Double-marker positivity	15.92	3.67–68.97	0.001	4.57	0.48–36.25	0.15	15.36	3.21–73.57	0.001
Mortality within 7 days									
Single-marker positivity	1.16	0.51–2.65	0.724	0.86	0.77–2.75	0.494	1.59	0.63–4.05	0.329
Double-marker positivity	2.75	1.34–5.65	0.006	4.1	1.41–11.78	0.001	2.01	0.75–5.40	0.166

A single-marker positivity was defined by the presence of [TIMP-2•IGFBP-7] above the cut-off of 0.3 or PCT above the cut-off of 0.5; the double-marker positivity was defined by the presence of [TIMP-2•IGFBP-7] measurements above 0.3 and the concomitant presence of PCT levels above 0.5
[TIMP-2•IGFBP-7]: tissue inhibitor metalloproteinases-2 and insulin-growth factor-binding protein-7 product; PCT: procalcitonin
a) Odds ratios (OR) were adjusted for Sequential Organ Failure Assessment (SOFA) and estimated glomerular filtration rate (eGFR) at the time of admission

Table 2. Patients' outcomes in the overall population and in septic and non-septic subgroups
Adapted from Godi I, et al. *Annals of Intensive Care* 2020;10:46

	Analysis cohort	Sepsis	Non-sepsis	*p*-value
Patients	433	181	252	
AKI at ICU admission	**26 (6.0)**	**14 (7.7)**	**12 (4.8)**	**0.001***
Stage 1	14 (3.2)	8 (4.4)	6 (2.4)	
Stage 2	5 (1.1)	2 (1.1)	3 (1.2)	
Stage 3	7 (1.6)	4 (2.2)	3 (1.2)	
AKI within 24 h	**149 (34.4)**	**82 (45.3)**	**67 (26.6)**	**<0.001***
Stage 1	46 (10.6)	25 (13.8)	21 (8.3)	
Stage 2	38 (8.8)	19 (10.5)	19 (7.5)	
Stage 3	65 (15.0)	38 (21.0)	27 (10.7)	
AKI within 48 h	**168 (38.8)**	**93 (51.4)**	**75 (29.8)**	**<0.001***
Stage 1	55 (12.7)	31 (17.1)	24 (9.5)	
Stage 2	44 (10.2)	22 (12.2)	22 (8.7)	
Stage 3	69 (15.9)	40 (22.1)	29 (11.5)	
RRT need	33 (7.6)	18 (9.9)	15 (6.0)	
AKD at 7 days	**47 (10.8)**	**26 (14.4)**	**21 (8.3)**	**<0.01***
Stage 0	15 (3.5)	10 (5.5)	5 (2.0)	
Stage 1	9 (2.1)	5 (2.8)	4 (1.6)	
Stage 2	7 (1.6)	4 (2.2)	3 (1.2)	
Stage 3	16 (3.7)	7 (3.9)	9 (3.6)	
RRT need	14 (3.2)	7 (3.9)	7 (2.8)	
7 days mortality	**65 (15.0)**	**37 (20.4)**	**28 (11.1)**	**<0.01***
ICU mortality	**100 (23.1)**	**50 (27.6)**	**50 (19.8)**	**0.57**
Days in ICU	**4 (2-11)**	**4 (2–10)**	**4 (2–11)**	**0.77**
Hospital mortality	**128 (29.6)**	**64 (35.4)**	**64 (25.4)**	**0.37**
Days in hospital	**15 (7–31)**	**13 (6–30)**	**15 (7–31)**	**0.27**

Data are reported as numbers (percentages) as categorical variables and median (interquartile range) for continuous variables. * identified a *p*-value <0.005
AKI: acute kidney injury; AKD: acute kidney disease; RRT: renal replacement therapy; ICU: intensive care unit.

CLICK TO ACCESS ARTICLE

CRITICAL CARE MEDICINE
2018;46(3):375-383

Kinetics of Urinary Cell Cycle Arrest Markers for Acute Kidney Injury Following Exposure to Potential Renal Insults.

Ostermann M, McCullough PA, Forni LG, Bagshaw SM, Joannidis M, Shi J, Kashani K, Honore PM, Chawla LS, Kellum JA.

OBJECTIVE

This study is an ancillary analysis of the multicenter Sapphire study, which examined the impact of exposure to common renal insults, such as major surgery, IV radiocontrast, vancomycin, nonsteroidal anti-inflammatory drugs, and piperacillin/tazobactam on the kinetics of the urinary biomarker [TIMP-2•IGFBP-7].

STUDY DESIGN

The kinetics of [TIMP-2•IGFBP-7] and serum creatinine were analyzed in 723 critically ill patients from the day prior to exposure up to 5 days after exposure.

RESULTS

Among these patients, 679 (94%) had at least one, 70% had more than one, and 35% had three or more exposures to a known renal insult.

CONCLUSIONS

There was a significant association between cumulative number of exposures up to study day 3 and risk of AKI (p=0.02), but no association between the specific type of exposure and AKI (p=0.22). With the exception of radiocontrast, patients who developed stage 2/3 AKI after one of the five exposures had a clear rise and fall of [TIMP-2•IGFBP-7] from the day of exposure to 24-48 hours later **(Figure 1)**.

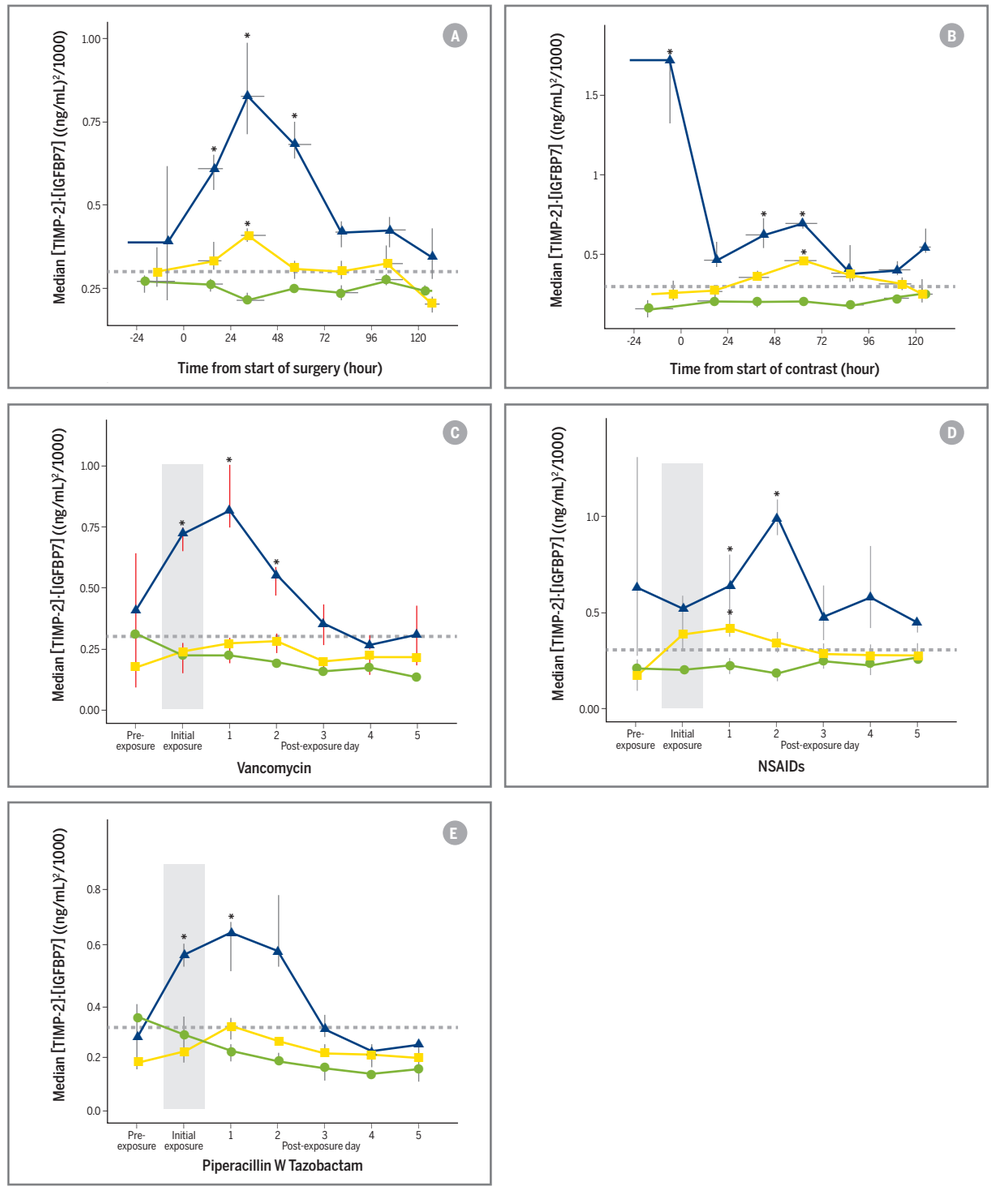
" Urinary [TIMP-2•IGFBP-7] exhibit a characteristic rise and fall around various exposures but importantly, only in patients who ultimately develop AKI."

KEY FINDINGS

- Exposure to multiple nephrotoxic insults is common during critical illness and associated with an increased risk of AKI.
- Serum creatinine is not altered during the early hours after exposure to a renal insult, but [TIMP-2•IGFBP-7] is typically elevated in patients who develop AKI.

URINARY BIOMARKERS [TIMP-2•IGFBP-7]

Figure 1. Biomarker kinetics in association with specific exposures
Adapted from Ostermann M, et al. *Critical Care Medicine* 2018;46(3):375-383



Time course of urinary [TIMP-2•IGFBP-7] concentrations relative to the time or day of exposure by acute kidney injury (AKI) stage for patients exposed to **(A)** major surgery, **(B)** IV contrast, **(C)** vancomycin, **(D)** nonsteroidal anti-inflammatory drugs (NSAIDs) or **(E)** piperacillin/tazobactam.

Symbols show median urinary [TIMP-2•IGFBP-7] concentrations for patients who had no AKI (circles), stage 1 AKI (squares), and stage 2/3 AKI (triangles) within 3 days post-exposure.

Vertical and horizontal lines through the symbols show the interquartile range of bootstrap medians for the [TIMP-2•IGFBP-7] concentrations and the time from exposure, respectively.

Median urinary [TIMP-2•IGFBP-7] concentrations are shown by day for drug exposures because only the day and not the time of exposure was recorded. The width of the shaded area indicates the day of the first dose of each drug.

CLICK TO ACCESS ARTICLE

JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY
2020;160(5):1235-1246.e2

Using urinary biomarkers to reduce acute kidney injury following cardiac surgery.

Engelman DT, Crisafi C, Germain M, Greco B, Nathanson BH, Engelman RM, Schwann TA.

OBJECTIVE

The objective of this study was to determine if therapeutic interventions driven by elevated urinary biomarkers reduce post cardiac surgical stage 2/3 Acute Kidney Injury (AKI).

STUDY DESIGN

A quality improvement initiative was undertaken based on adding urinary biomarkers (UB) and an Acute Kidney Response Team (AKRT) to standard of care patient management.

The study used cell cycle arrest urinary biomarkers: tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7). Cell cycle arrest is described as "kidney stress", and occurs before kidney damage.

All adult patients >18 years' old with a preoperative serum creatinine level <2.0 mg/dL undergoing a cardiac operation with cardiopulmonary bypass between July 2016 and June 2018 were included. Data from the Society of Thoracic Surgeons (STS) Adult Cardiac Database were retrospectively reviewed.

Outcomes were compared between patients undergoing cardiac surgery before the use of UB (pre-UB) between July 2016 and June 2017 and after implementation of the quality improvement initiative (instituted on July 1, 2017) for the following year: July 2017 to June 2018 (post-UB). The primary study endpoint was the development of stage 2 or 3 AKI.

Urinary biomarkers were measured in the morning after cardiac surgery. In the post-UB period, the multidisciplinary AKRT, composed of intensivists, nephrologists, cardiac surgeons, nurses, and advanced practitioners, was triggered in UB-positive (>0.3) patients. AKRT used a predetermined algorithm based on the KDIGO cardiac surgery care bundle. This bundle includes targeted goal directed fluid management, liberalizing transfusion thresholds, continued invasive hemodynamic monitoring, and avoidance of nephrotoxins.

A pocket card was used by the multidisciplinary team to guide the systematic response to the UB results **(Figure 1)**.

RESULTS

A total of 435 patients in the pre-UB group were compared to 412 patients in the post-UB cohort with respect to incidence of stage 2/3 AKI. Of the post-UB patients, 55% had a moderate or high UB score (≥0.3 ng/dL). In the pre-UB group, 10 (2.30%) had stage 2/3 AKI vs 1 (0.24%) post-UB, representing an 89% relative reduction (p=0.01) **(Figures 2 and 3)**. Total and postoperative length of stay, cost, mortality and readmissions were found to be similar between groups. The negative predictive value for AKI of UB <0.3 ng/dL was 100%.

CONCLUSIONS

A multidisciplinary AKRT triggered by urinary biomarkers for kidney stress reduced acute kidney injury following cardiac surgery. Findings suggest that routine measurement of UB values may be useful in identifying cardiac surgery patients at risk for perioperative AKI, and the subsequent activation of an AKRT with implementation of an AKI bundle may be a beneficial adjunct to routine clinical care in preventing stage 2/3 AKI. While labor-intensive, these interventions were not associated with increased length of stay or higher costs.

"…. UB [urinary biomarkers] may alert clinicians to implement preventative and protective measures in patients at high-risk for AKI long before clinical AKI manifests."

KEY FINDINGS

- Early urinary biomarkers [TIMP-2•IGFBP-7] triggered implementation of an Acute Kidney Response Team utilizing a KDIGO "cardiac surgery care bundle", which resulted in an 89% relative decrease in the incidence of moderate or severe AKI within 7 days of surgery compared to routine post-operative clinical care.
- The routine measurement of urinary biomarkers and subsequent activation of an acute kidney response team are useful additions to the conventional post-cardiac surgery therapy.

Figure 1. Pocket card for the acute kidney response team: urinary biomarker (UB) (NEPHROCHECK®) values and corresponding response

Adapted from Engelman DT, et al. *Journal of Thoracic and Cardiovascular Surgery* 2020;160(5):1235-1246.e2

Acute Kidney Response Team Pocket Card

THE NEPHROCHECK® TEST

Intended to aid in assessing the risk of moderate to severe AKI.

WHO TO TEST

All cardiac surgery patients on post-op day 1 at 05:30.

WHO NOT TO TEST

Pre-op creatinine >2, on dialysis or received methylene blue.

STAGE OF ACUTE KIDNEY INJURY (AKI)

	Serum Creatinine	Urine Output
2	Increase of 2.0 - 2.9 x baseline	<0.5 ml/kg/h for 12 hours
3	Increase of >3x baseline or increase of SCr to >4 mg/dL or initiation of RRT	<0.3 ml/kg/h for 24 h or anuria for 12 hours

WHEN & HOW TO TEST

1. Patient meets test inclusion: at 05:30 am PO DI collect fresh urine specimen from Foley bag (at least 10 ml).
2. Results will show up in EMR chemistry section under urine miscellaneous - click for value range. Lab will report results in time for HVCC 07:00 team rounds.

NC/ACUTE KIDNEY RESPONSE TEAM (AKRT) 2.0

NEG <0.3	(+) 0.3-2.0	HIGH (+) >2.0
FAST TRACK	**TELE UNIT @ 4PM**	**ACTIVATE AKRT**
Remove Foley, arterial line, central line. Transfer to telemetry if meeting all other criteria (CI/HR/Resp. fxn) liberal diuretics.	Keep Foley and monitor hourly UO until afternoon rounds. Transfer to telemetry (alter 4PM) if all other transfer criteria are met (CI/HR/Resp. fxn) and no oliguria treatment was required.	Keep Foley and monitor hourly UO. Maintain hemodynamic monitoring.
MAY USE: ARBs/ACE-I, Toradol prn (if pre-op GFR>60) Consider holding diuretics if Toradol given.	**AVOID NEPHROTOXINS** NSAIDS, ARBs/ACE-I, Vanco/Gentamycin Transfusion threshold hemoglobin <7.0 unless oliguric.	**AVOID NEPHROTOXINS** NSAIDS, ARBs/ACE-I, Vanco/Gentamycin Renal dosing of medications.
Transfusion threshold hemoglobin <7.0 Check SCr daily	**IF PT BECOMES OLIGURIC:** (UO <0.5 cc/kg/hr X 3 hours) activate AKRT/Nephrology consult. Use lactated ringers boluses if CVP<8; PAD<14; Hold Lasix unless pulmonary edema. Repeat NC in 24hr	Goal directed therapy (keep PAD>14 with LR, No diuretics unless PAD>20 or CHF), reassess transfusion threshold. CI >2.5, SBP>130. Monitor SVO_2. Echo if <55% Nephrology Consult Repeat NC in 24hr

AKI: Acute kidney injury; SCr: serum creatinine; RRT: renal replacement therapy; EMR: electronic medical record; HVCC: Heart&Vascular Critical Care Unit; AKRT: acute kidney response team; CI: cardiac index; HR: heart rate; ARB: angiotensin II receptor blocker; ACE-I: angiotensin-converting-enzyme inhibitor; GFR: glomerular filtration rate; NSAIDS: nonsteroidal anti-inflammatory drugs; CVP: central venous pressure; PAD: pulmonary artery diastolic pressure; CHF: congestive heart failure; SBP: systolic blood pressure; SVO_2: mixed venous oxygen saturation.

Figure 2. Prevalence of cardiac surgery–associated AKI before and after use of the urinary biomarker (NEPHROCHECK®), demonstrating an 89% reduction in moderate/severe AKI after introducing the biomarker

Adapted from Engelman DT, et al. *Journal of Thoracic and Cardiovascular Surgery* 2020;160(5):1235-1246.e2

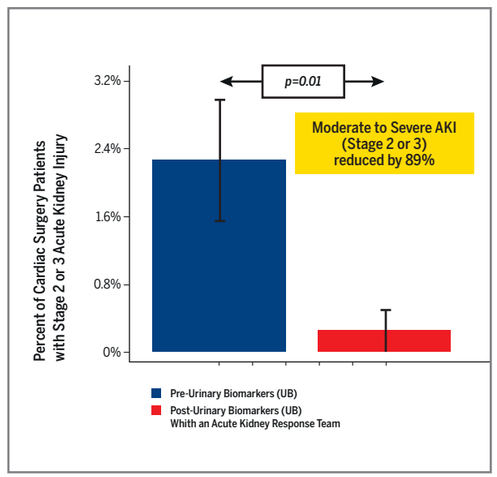
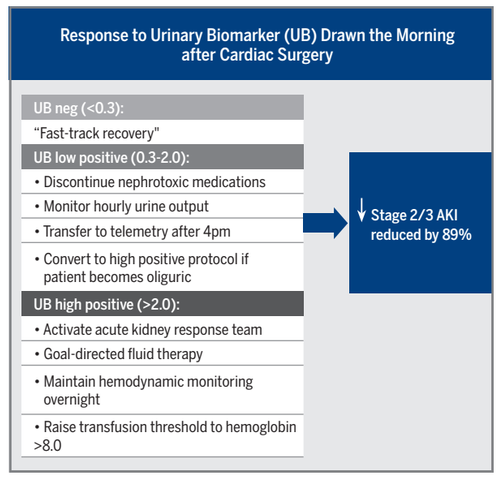


Figure 3. Responses to negative (<0.3), low positive (0.3-2.0), and high positive (>2.0), urinary biomarker values (NEPHROCHECK®) on the morning after surgery and the resultant decrease in stage 2/3 acute kidney injury

Adapted from Engelman DT, et al. *Journal of Thoracic and Cardiovascular Surgery* 2020;160(5):1235-1246.e2



CLICK TO ACCESS ARTICLE

JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY
2019;157(4):1545-1553.e5

Intraoperative prediction of cardiac surgery-associated acute kidney injury using urinary biomarkers of cell cycle arrest.

Cummings JJ, Shaw AD, Shi J, Lopez MG, O'Neal JB, Billings FT.

OBJECTIVE

Investigators tested the hypothesis that intraoperative concentrations of urinary [TIMP-2•IGFBP-7] are associated with postoperative AKI.

STUDY DESIGN

This was a prospective cohort study from a previously published trial of statin therapy for prevention of AKI in cardiac surgery. The Statin AKI Cardiac Surgery trial was a randomized, double-blinded, placebo-controlled trial to test the efficacy of perioperative atorvastatin administration for reducing cardiac surgery-associated AKI (CSA-AKI).

Adult patients undergoing elective coronary bypass grafting, valvular heart surgery, or ascending aortic surgery at Vanderbilt University Medical Center were eligible for inclusion. Eight perioperative measurements of [TIMP-2•IGFBP-7] were performed.

The primary endpoint was stage 2/3 (moderate-severe) AKI occurring within 48 hours of surgery, defined by changes in serum creatinine according to KDIGO criteria.

RESULTS

The study included 400 patients, of whom fourteen patients (3.5%) developed stage 2/3 AKI within 48 hours of surgery, and a further 77 patients (19.3%) developed stage 1 AKI.

Patients who developed stage 2/3 AKI displayed 2 elevation peaks of [TIMP-2•IGFBP-7] - intraoperatively and six hours postoperatively. The time course was characterized by [TIMP-2•IGFBP-7] that increased significantly immediately after the end of CPB or off-pump coronary artery bypass (OpCAB), returned towards baseline at ICU admission, and then subsequently increased considerably more six hours after ICU admission. [TIMP-2•IGFBP-7] levels then remained elevated into postoperative day 1 before decreasing towards baseline on postoperative day 2 in stage 2/3 AKI patients compared to patients with stage 1 or no AKI **(Figure 1)**.

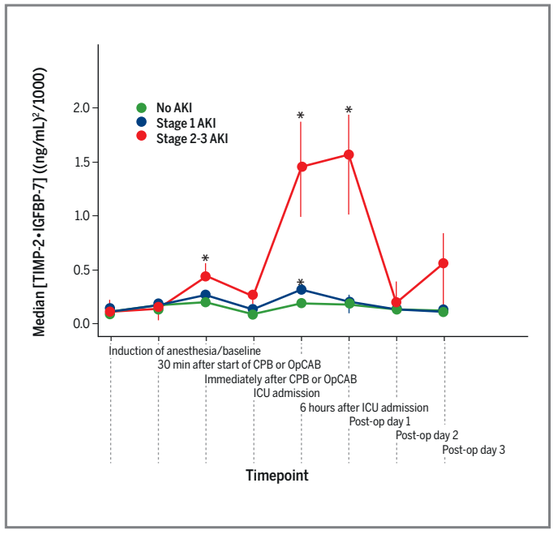
Each 10-fold increase in intraoperative [TIMP-2•IGFBP-7] was found to be independently associated with a 290% increase in the odds of stage 2/3 AKI (p=0.01), and each 10-fold increase in six hours postoperative [TIMP-2•IGFBP-7] with a 650% increase (p<0.001). The maximum [TIMP-2•IGFBP-7] between these two time points provided an area under the curve (AUC) of 0.82 (95% CI: 0.73–0.90), 100% sensitivity, and 100% negative predictive value using the >0.3 cutoff to predict stage 2/3 AKI.

No elevations in [TIMP-2•IGFBP-7] were observed in patients who did not develop AKI.

CONCLUSIONS

Increased intraoperative concentrations and increased early postoperative concentrations of [TIMP-2•IGFBP-7] are independently associated with development of moderate-severe AKI. Perioperative [TIMP-2•IGFBP-7] is a highly sensitive predictor of postoperative AKI and could provide the opportunity to alter postoperative management to prevent kidney injury.

"If either the intraoperative or the early postoperative [TIMP-2•IGFBP-7] is >0.3, we recommend instituting renal supportive measures such as the KDIGO bundle."



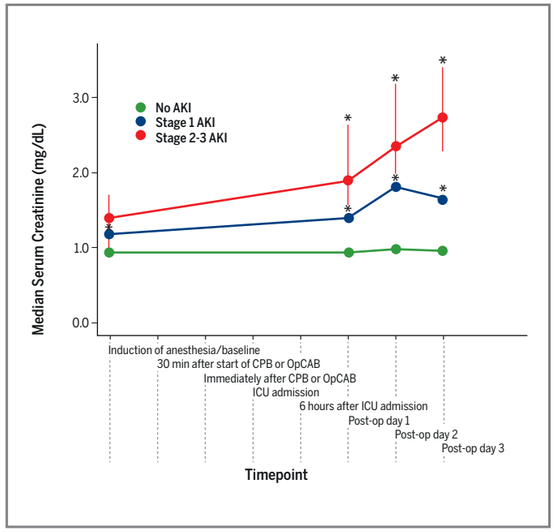


Figure 1. Median perioperative urinary [TIMP-2•IGFBP-7] and serum creatinine concentrations in patients with No AKI (green), Stage 1 AKI (blue), and Stage 2/3 AKI (red)

Adapted from Cummings JJ, et al. *Journal of Thoracic and Cardiovascular Surgery* 2018;157(4):1545-1553.e5

Intraoperative elevations of [TIMP-2•IGFBP-7] can predict moderate-severe AKI and could provide opportunity to alter post-operative management to prevent kidney injury.

Vertical lines through the symbols show the interquartile range of bootstrap medians for the [TIMP-2•IGFBP-7] and creatinine concentrations.
*p<0.05 for comparing the distributions of [TIMP-2•IGFBP-7] or creatinine values to the distributions among patients without AKI.

KEY FINDINGS

- In patients who were later diagnosed with stage 2/3 AKI, there was a bimodal elevation where initial urinary [TIMP-2•IGFBP-7] was increased during surgery followed by a decrease at ICU admission and then a sharp increase within six hours.
- If neither the intraoperative nor the early postoperative test is positive (>0.3), the treating clinician may be confident the patients will not develop moderate-severe AKI (the "double-negative" [TIMP-2•IGFBP-7]).
- The negative predictive value using this sampling strategy in the study was 100% and sensitivity of 100% using the >0.3 cutoff.

CLICK TO ACCESS ARTICLE

INTENSIVE CARE MEDICINE
2017;43(11):1551-1561

Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial.

Meersch M, Schmidt C, Hoffmeier A, Van Aken H, Wempe C, Gerss J, Zarbock A.

OBJECTIVE

This single-center randomized controlled trial (RCT) investigated whether the "KDIGO bundle" could reduce the occurrence and severity of acute kidney injury (AKI) in patients post cardiac surgery.

STUDY DESIGN

Control patients received standard care treatment and intervention patients received the care "bundle," consisting of optimization of volume status and hemodynamics, avoidance of nephrotoxic drugs, and prevention of hyperglycemia. High-risk patients were defined as those with urinary biomarker [TIMP-2•IGFBP-7] >0.3. The primary endpoint was the rate of AKI defined by KDIGO criteria within the first 72 h after surgery. Secondary endpoints included AKI severity, need for dialysis, length of stay, and major adverse kidney events (MAKE) at days 30, 60, and 90.

RESULTS

Overall incidence of AKI was 63.4% (175/276). The intervention group had significantly lower rates of AKI (55.1%) compared to controls [71.7%; p=0.004] **(Figure 1)**. Rates of moderate to severe AKI were also significantly reduced by the intervention compared to controls. The implementation of the bundle resulted in significantly improved hemodynamic parameters at different time points (p<0.05), less hyperglycemia (p<0.001) and reduced use of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs) (p<0.001) compared to controls. Other secondary outcomes did not vary significantly between groups.

CONCLUSIONS

This study observed that by identifying high-risk patients using the urinary biomarker [TIMP-2•IGFBP-7], a bundle of supportive measures could be implemented which reduced the occurrence of AKI within 72 hours compared to standard care.

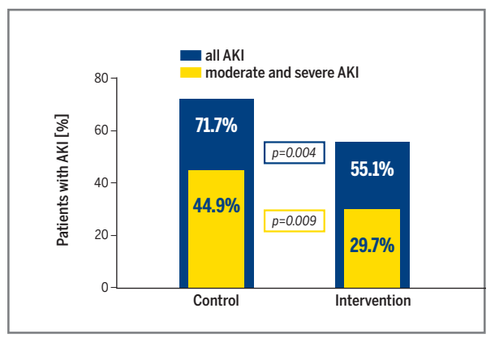


Figure 1. Occurrence of cardiac surgery-associated AKI (CSA-AKI) and rate of CSA-AKI in control and intervention groups
Adapted from Meersch et al. *Intensive Care Medicine* 2017;43(11):1551-1561

"Biomarkers may allow one to implement preventive and protective measures well before clinical AKI becomes manifest according to well-established definitions."

KEY FINDINGS

- In this RCT of patients undergoing cardiac surgery, the urinary [TIMP-2•IGFBP-7] biomarker identified high-risk patients, which allowed for the implementation of a bundle of protective measures and reduced the occurrence of AKI within 72 hours compared to standard care.
- In high-risk cardiac surgery patients, implementing the KDIGO care bundle guidelines compared with standard care may reduce the frequency and severity of AKI after cardiac surgery in high-risk patients.

HEALTH ECONOMICS AND OUTCOMES STUDIES

CLICK TO ACCESS ARTICLE

JOURNAL OF MEDICAL ECONOMICS
2019;22(12):1281-1289

Economic and clinical benefits of early indication of acute kidney injury using a urinary biomarker.

Berdugo MA, Noam Y. Zimmer L, Beyhaghi H, Toback S, Scarpati LM, Stone MN, Dember R, Tseng-Tham J, Wen J, Miller M.

OBJECTIVE

The purpose of this study was to evaluate the incremental budget impact of adding a novel diagnostic test, [TIMP-2•IGFBP-7], which identifies patients at risk of moderate to severe acute kidney injury (AKI), to the current standard of care (SOC) in a hospital setting. Through more rapid identification of AKI risk and treatment, overall AKI severity and healthcare utilization could be reduced.

STUDY DESIGN

A budget impact model was developed from the perspective of a hypothetical US hospital system serving 10,000 inpatients annually. Using published data and expert opinion, the model estimated the effect of adding the US Food and Drug Administration approved assay [TIMP-2•IGFBP-7] to SOC on healthcare utilization and costs over a 1-year time horizon. Other factors that had cost implications included payer mix among patients, diagnostic efficacy, and provider adoption rates as well as biomarker costs.

RESULTS

As compared to SOC alone, adding [TIMP-2•IGFBP-7] to SOC was associated with a $1,855 reduction in uncompensated care per patient tested, which, after accounting for the additional costs of the test, resulted in annual net savings of $1,578 per patient tested and hospital savings of $789,104 (2017 USD) **(Table 1)**. In varying model parameters, net cost savings to the hospital ranged from $50,308 to $3,971,514, or $101 to $7,943 per tested patient (mean $1,710; 95% confidence interval $1,691–$1,729).

CONCLUSIONS

Adding [TIMP-2•IGFBP-7] to SOC risk assessment for AKI could lead to substantial cost-savings for the hospital, largely by resulting in shorter ICU and non-ICU lengths of stay and fewer 30-day readmissions **(Table 2)**.

Prospective real-world studies are needed to evaluate the effect of [TIMP-2•IGFBP-7] on patient outcomes and healthcare costs.

"The introduction of [TIMP-2•IGFBP-7] as a novel tool in the identification of AKI risk may result in considerable cost savings from a hospital perspective under this model's base-case assumptions."

KEY FINDINGS

- The use of [TIMP-2•IGFBP-7] to identify acute kidney injury risk may reduce costs for hospitals by approximately $1,578 per patient tested.
- Adding [TIMP-2•IGFBP-7] as a novel tool may decrease time to identification of AKI risk, treatment and may result in shorter lengths of stay, fewer 30-day readmissions and overall hospital costs.

HEALTH ECONOMICS AND OUTCOMES STUDIES

Table 1. Annual net savings by level of AKI severity (overall and per tested patient)

Adapted from Berdugo MA, et al. *Journal of Medical Economics* 2019;22(12):1281-1289

	No AKI	Mild	Moderate	Severe	Total
Per tested patient	-$1,227	$0	$2,126	$956	**$1,578**
Overall	-$613,311	$0	$1,063,149	$477,766	**$789,104**

Total cost is inclusive of the incremental per-usage estimate for [TIMP-2•IGFBP-7]. Monetary values are in 2017 United States dollars.
Abbrevations. AKI: acute kidney injury.

Table 2. Reduction in overall clinical burden and resulting budget impact by AKI severity (overall and per patient)

Adapted from Berdugo MA, et al. *Journal of Medical Economics* 2019;22(12):1281-1289

Overall reduction in health care resource utilization among target population	No AKI	Mild	Moderate	Severe	Total
Total ICU bed under SOC	181	264	146	70	**661**
Total ICU bed with SOC and [TIMP-2•IGFBP-7]	232	264	50	24	**570**
Decrease in ICU bed with [TIMP-2•IGFBP-7]	-51	0	96	46	**91**
Total non-ICU bed under SOC	465	775	319	136	**1,696**
Total non-ICU bed with SOC and [TIMP-2•IGFBP-7]	597	775	109	46	**1,527**
Decrease in non-ICU bed with [TIMP-2•IGFBP-7]	-131	0	211	90	**170**

Resulting budget impact due to reduced uncompensated care among target population	No AKI	Mild	Moderate	Severe	Total
Total ICU costs under SOC	$905,100	$1,322,475	$729,675	$349,590	**$3,306,840**
Total ICU costs with SOC and [TIMP-2•IGFBP-7]	$1,160,085	$1,322,475	$248,164	$118,896	**$2,849,619**
ICU savings with addition of [TIMP-2•IGFBP-7] to SOC	- $254,985	$0	$481,511	$230,694	**$457,221**
Total non-ICU costs under SOC	$1,163,700	$1,937,513	$798,413	$341,205	**$4,240,830**
Total non-ICU costs with SOC and [TIMP-2•IGFBP-7]	$1,491,538	$1,937,513	$271,541	$116,044	**$3,816,636**
Non-ICU, inpatient savings with addition of [TIMP-2•IGFBP-7] to SOC	- $327,838	$0	$526,871	$225,161	**$424,194**
Total readmission costs under SOC	$108,224	$167,360	$82,993	$33,205	**$391,781**
Total readmission costs with SOC and [TIMP-2•IGFBP-7]	$138,713	$167,360	$28,226	$11,293	**$345,591**
Savings on 30-day readmissions with addition of [TIMP-2•IGFBP-7] to SOC	-$30,489	$0	$54,767	$21,912	**$46,189**
Total cost of uncompensated care under SOC	$2,177,024	$3,427,347	$1,611,080	$724,000	**$7,939,451**
Total cost of uncompensated care with SOC and [TIMP-2•IGFBP-7]	$2,790,335	$3,427,347	$547,931	$246,233	**$7,011,846**
Savings on uncompensated care with addition of [TIMP-2•IGFBP-7] to SOC	-$613,311	$0	$1,063,149	$477,766	**$927,604**
Per-tested-patient savings on uncompensated care with addition of [TIMP-2•IGFBP-7] to SOC	-$1,227	$0	$2,126	$956	**$1,855**

Monetary values are in 2017 United States dollars. Abbrevations. AKI: acute kidney injury; ICU: intensive care unit; SOC: standard of care.

CLICK TO ACCESS ARTICLE

CRITICAL CARE MEDCINE
2019;47(10):E820-E826

Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury.

Joannidis M, Forni LG, Haase M, Koyner J, Shi J, Kashani K, Chawla LS, Kellum JA, on behalf of the Sapphire Investigators.

OBJECTIVE

This paper describes a secondary analysis of the Sapphire trial, an international, prospective, observational study[1] which evaluated two biomarkers of G1 cell cycle arrest, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein-7 (IGFBP-7) for AKI risk assessment. In the primary analysis, these two biomarkers were found to be superior to other existing biomarkers, provide additional information over clinical variables and add mechanistic insight into AKI.

The purpose of this secondary analysis was to evaluate whether adding [TIMP-2•IGFBP-7] to serum creatinine (SCr), and urine output (UO) improves risk prediction for development of stage 3 AKI, need for dialysis, or death within one week of enrollment. Longer-term outcomes were also examined: the relationship between [TIMP-2•IGFBP-7] measurements and death or dialysis within nine months in patients who progressed to stage 2-3 AKI within one week.

STUDY DESIGN

This study included subjects from the prospective Sapphire trial who did not have stage 2-3 AKI at enrollment. Among 661 subjects eligible for this analysis, urine samples for testing with biomarkers [TIMP-2•IGFBP-7] were collected at enrollment and at 12-hour intervals up to 30 hours. AKI status based on SCr and UO were determined within ±12 hours of biomarker sample collection.

RESULTS

Among the 79 patients (10.9%) who died or had stage 3 AKI, including dialysis over the first week, 50 patients died; and 41 had stage 3 AKI, of whom 26 received dialysis. These patients were more likely to be surgical patients and to have higher non-renal APACHE[2] III scores, which measures hospital mortality risk in critically ill patients.

Among patients who had more than one positive variable indicating AKI, (stage 1 SCr, stage 1 UO and [TIMP-2•IGFBP-7] results (2.0)), the risk of stage 3 AKI or death doubled for patients with two positive results indicating AKI and rose by over 16 times when all 3 variables were positive **(Figures 1 and 2)**.

CONCLUSIONS

Biomarkers of cell cycle arrest, [TIMP-2•IGFBP-7], in conjunction with SCr and/or UO, improve risk stratification for severe outcomes among patients with stage 1 AKI. Patients with [TIMP-2•IGFBP-7] values above 2.0 had increased risk of death or dialysis at 9 months **(Figure 3)**.

1. Kashani K, et al. Critical Care 2013;17(1):R25 (see page 16)
2. APACHE: Acute Physiology and Chronic Health Evaluation

"Cell cycle arrest biomarkers, TIMP-2 and IGFBP-7, improve risk stratification for severe outcomes in patients with stage 1 acute kidney injury by urine output, serum creatinine or both, with risk increasing with each acute kidney injury indicator."

KEY FINDINGS

- Patients who develop stage 1 AKI are at high risk of progressing to stage 3 AKI.
- Risk for stage 3 AKI or death increases with each indicator of AKI: SCr, UO and [TIMP-2•IGFBP-7] measurement greater than 2.0.

Figure 1A and 1B. Stage 3 acute kidney injury (AKI) or death by AKI status by SCr and [TIMP-2•IGFBP-7] level relative to the 0.3 (A) and 2.0 (B) cutoffs.
Adapted from Joannidis M, et al. *Critical Care Medicine* 2019;47(10):e820-e826

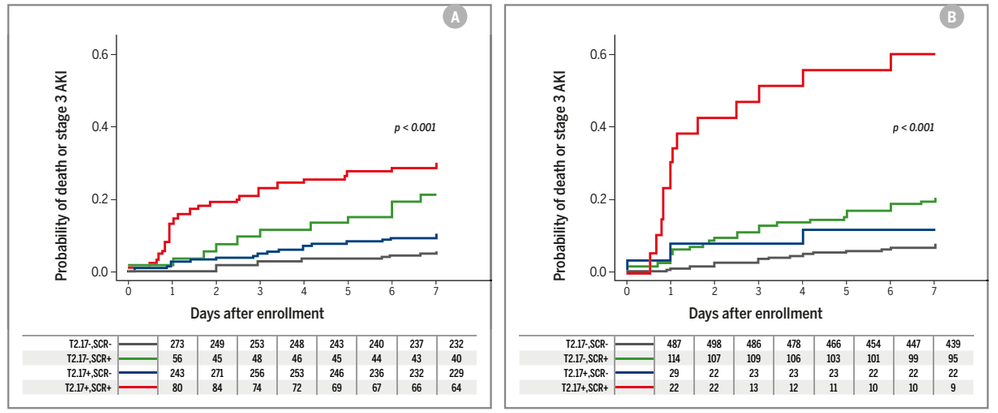


Figure 2A and 2B. Stage 3 acute kidney injury (AKI) or death by AKI status by UO and [TIMP-2•IGFBP-7] level relative to the 0.3 (A) and 2.0 (B) cutoffs.
Adapted from Joannidis M, et al. *Critical Care Medicine* 2019;47(10):e820-e826

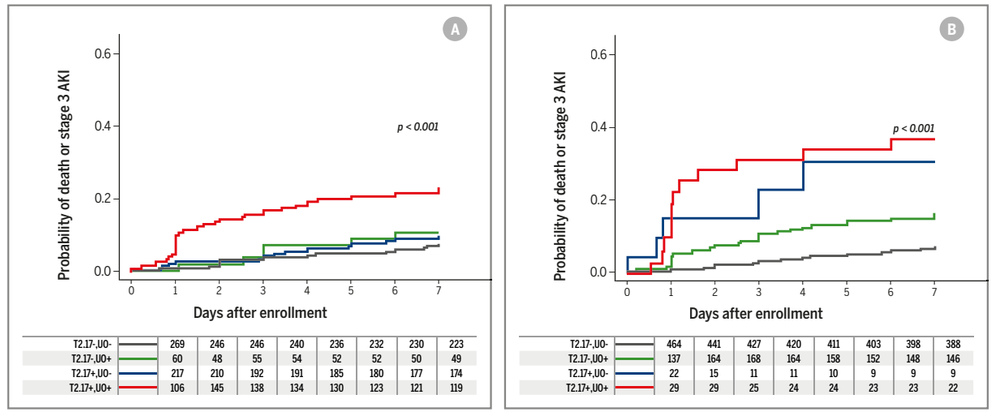
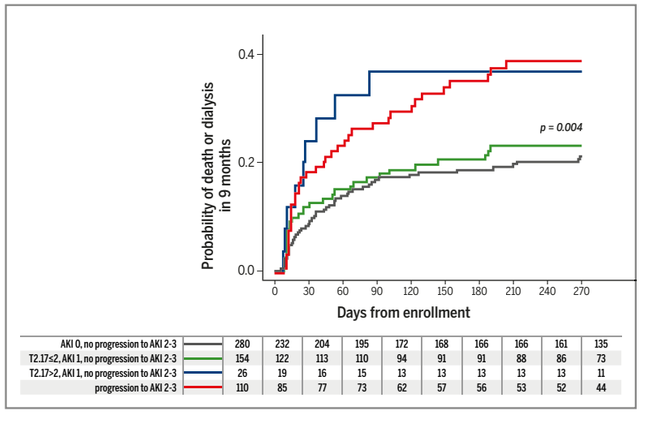


Figure 3. Death or dialysis within 9 months among patients who were alive and dialysis free at 7 days after enrolment.
Adapted from Joannidis M, et al. *Critical Care Medicine* 2019;47(10):e820-e826



CLICK TO ACCESS ARTICLE

ANNALS OF SURGERY
2018;267(6):1013-1020

Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study.

Göcze I, Jauch D, Götz M, Kennedy P, Jung B, Zeman F, Gnewuch C, Graf BM, Gnann W, Banas B, Bein T, Schlitt HJ, Bergler T.

OBJECTIVE

This prospective, randomized single-center study assessed the impact of renal biomarker-guided implementation of the Kidney Disease: Improving Global Outcomes (KDIGO) care bundle on acute kidney injury (AKI) incidence in patients admitted to the intensive care unit (ICU) after major non-cardiac surgery.

STUDY DESIGN

Patients who had intraoperatively received a jugular central venous line and a urinary catheter and had at least one additional risk factor for AKI were screened with the urine biomarker [TIMP-2•IGFBP-7]. Other risk factors included age >75 years, critical illness, pre-existing chronic kidney disease or intraoperative use of an intravenous radiocontrast agent.

One hundred and twenty-one (121) patients with a [TIMP-2•IGFBP-7] value above 0.3 within 4 hours of ICU admit were randomized 1:1 to standard care treatment (n=61) or the KDIGO care bundle (n=60). Patients were stratified by [TIMP-2•IGFBP-7] level: >0.3-2.0 and >2.0. The control group received standard of care treatment including a weekly assessment of medications. Patients in the intervention group received the KDIGO care bundle, including continuous intravenous fluid administration for 6 hours along with nephrology consultation.

The primary endpoint was incidence of AKI during the first 7 days after surgery. Severity of AKI, length of stay (LOS), major kidney events at discharge, and cost effectiveness were also evaluated.

RESULTS

In the intervention group, 31.7% of patients were classified as having AKI versus 47.5% in the control group. This difference was not statistically significant. However, in the 0.3-2.0 cohort receiving the care bundle, reduction in AKI incidence was statistically significant compared to controls (27.1% versus 48%, p=0.03).

Biomarker guided care also significantly reduced the incidence of moderate and severe AKI in the intervention group (6.7% versus 19.7%, p=0.04). Median ICU LOS decreased by 1 day in the intervention group and median hospital LOS declined by 5 days. Reducing the ICU LOS by 1 day was associated with a cost savings of £2,031 per patient. Additionally, the relative decrease in urinary biomarker levels 12 hours after surgery was significantly greater in the intervention group, with the greatest declines in the 0.3-2.0 level group.

CONCLUSIONS

Early implementation of the KDIGO care bundle based on biomarker-based prediction of imminent AKI significantly reduced the incidence of moderate and severe AKI. Furthermore, postoperative creatinine increases were reduced, along with shorter length of ICU and hospital stay in patients after major non-cardiac surgery, resulting in ICU cost-savings.

"Reducing the incidence and severity of AKI... was caused by prediction of imminent AKI at the very early stage."

KEY FINDINGS

- Early identification of AKI risk and use of the KDIGO care bundle significantly reduces AKI severity and hospital and ICU LOS.
- Intervening early in patients with [TIMP-2•IGFBP-7] levels 0.3-2.0 showed the greatest impact on outcomes, possibly because patients in this range had preventable AKI while patients with higher [TIMP-2•IGFBP-7] levels may have established AKI.

GUIDELINES AND CONSENSUS STATEMENTS

CLICK TO ACCESS ARTICLE

THE JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION
2020;3(10):E2019209

Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference.

Ostermann M, Zarbock A, Goldstein S.

This 23rd edition of Acute Disease Quality Initiative (ADQI) is a follow-up consensus meeting from the 10th ADQI in 2011, where the consensus was that there was limited data on novel biomarkers and their use in practice. Since then, new AKI biomarkers have been discovered, evaluated in clinical trials, and some biomarkers have gained official regulatory approval. These include urinary biomarkers, [TIMP-2•IGFBP-7], which are early indicators of kidney injury or stress. There was therefore a need to review this new evidence and develop appropriate recommendations for the use of these AKI biomarkers in routine clinical practice.

This 23rd edition utilized the work of a panel of 23 experts from the fields of nephrology, critical care medicine, surgery, anesthesia, pediatrics and pharmacy. A wide array of publications were assessed and recommendations were made from a 90% consensus amongst the panelists. The panel produced 11 consensus statements for biomarker use each with an associated grade using the Grading of Recommendations, Assessment, Development and Evaluation system. Consensus statements include recommendations related to the following:

- Biomarkers for AKI risk assessment
- Biomarkers for AKI prediction and prevention
- Biomarkers for AKI diagnosis, etiology and management
- Biomarkers to assess AKI progression and kidney recovery.

Specifically regarding urinary biomarkers, [TIMP-2•IGFBP-7], the Consensus Statement recommends:

- using these biomarkers to identify patient populations at risk of developing AKI and for whom preventive interventions have been shown to improve outcomes. Trials (PrevAKI, BigpAK) have demonstrated that initiating timely preventive strategies in patients with positive stress biomarker results after a kidney insult can be effective at preventing AKI.
- using both functional and stress/damage biomarkers concomitantly to optimize dosing and duration of treatment with life-saving, but potentially nephrotoxic drugs and to prevent AKI.
- combining clinical assessment and these newly validated biomarkers to triage patients, improve risk stratification in critically ill patients, and optimize the timing and type of interventions designed to improve patient management and outcomes. This combined approach provides information that may support changes in care processes and guide therapy.

CONCLUSIONS

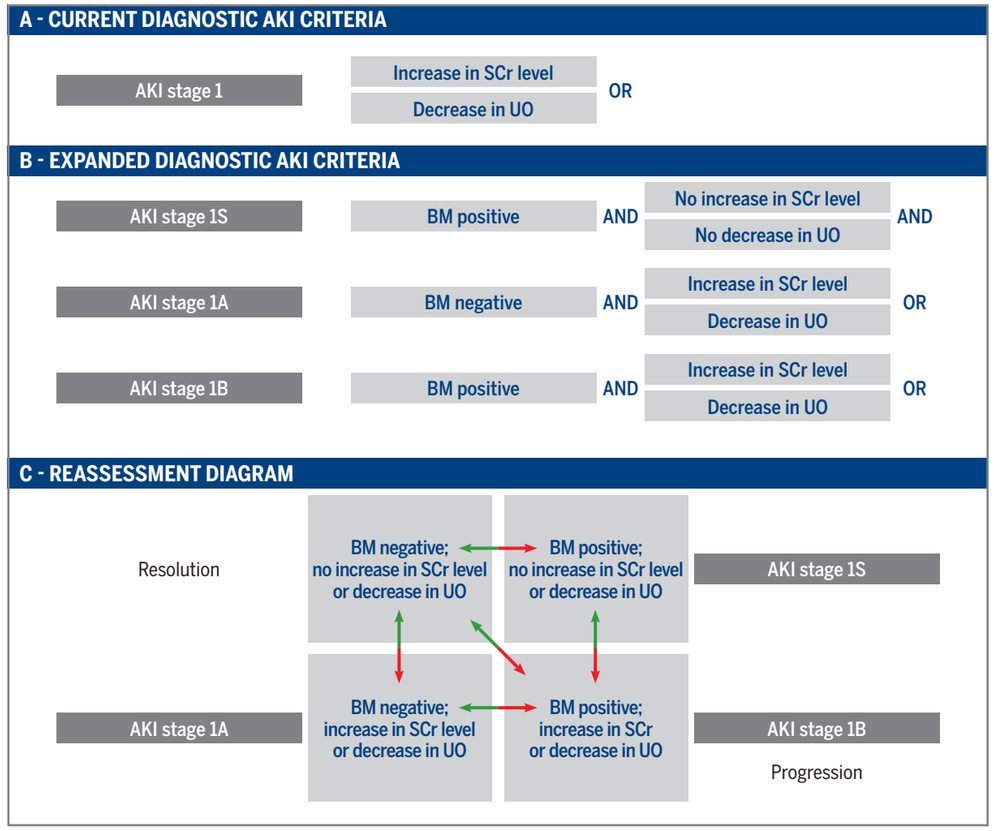
Progress made in the field of AKI biomarkers over the past decade has led to improved outcomes through biomarker-guided algorithms and goal-directed management protocols. Evidence from clinical trials substantiates the routine use of new biomarkers for AKI prevention and management. By indicating kidney stress before permanent damage occurs, these new biomarkers support the possibility of reversing AKI and positively impacting patient recovery. The consensus recommendations of this 23rd ADQI meeting aim to support clinicians in the use of these biomarkers in their daily practice. Gaps in knowledge remain and more research is needed to further improve management of AKI.

"... the prospect of clearer identification of high-risk patients and different AKI sub-phenotypes and the integration of appropriately selected biomarkers in routine clinical practice hold the key to further improvement in AKI care."

KEY FINDINGS

- Current evidence from clinical trials support the use of biomarkers for management and prevention of AKI.
- Several novel biomarkers can detect AKI earlier and with more sensitivity when compared to serum creatinine.
- The integration of such novel biomarkers in routine clinical practice has the potential to improve acute kidney injury care.
- The use of validated biomarkers is recommended to identify patient populations for whom preventive interventions have been shown to improve outcomes.

Figure 1. Refined Staging System for the diagnosis of Acute Kidney Injury (AKI).
Adapted from Ostermann M, et al. *The Journal of the American Medical Association* 2020;3(10):e2019209



AKI: acute kidney injury; BM: biomarker; SCr: serum creatinine; UO: urine output

Patients with a biomarker of injury positivity without increase or decrease in SCr level and not reaching UO criteria should be classified as 1S. Reassessment should be performed according to patient clinical context and temporal trends. Patients reaching SCr and UO criteria with no increase on BM are defined as stage 1A, and those reaching SCr and UO criteria with increased BM are reclassified as stage 1B. BM positivity should be based on its mechanism an defined threshold.

Figure 2. Proposed new definition of Acute Kidney Injury.
Adapted from Ostermann M, et al. *The Journal of the American Medical Association* 2020;3(10):e2019209

FUNCTIONAL CRITERIA	STAGE	DAMAGE CRITERIA
No change or SCr level increase <0.3 mg/dL and no UO criteria	1S	Biomarker positive
Increase of SCr level by ≥0.3 mg/dL for ≤48 h or ≥150% for ≤7 days and/or UO <0.5 mL/kg/h for >6 h	1A	Biomarker negative
	1B	Biomarker positive
Increase of SCr level by >200% and/or UO <0.5 mL/kg/h for >12 h	2A	Biomarker negative
	2B	Biomarker positive
Increase of SCr level by >300% (≥4.0 mg/dL with an acute increase of ≥0.5 mg/dL) and/or UO <0.3 mL/kg/h for >24 h or anuria for >12 h and/or acute KRT	3A	Biomarker negative
	3B	Biomarker positive

KRT: kidney replacement therapy; SCr: serum creatinine; UO: urine output
Functional markers include SCr and UO but new functional markers may also be included.

NATURE REVIEWS NEPHROLOGY
2020;16(12):747-764

COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup.

Nadim M, Forni L, Mehta R.

The novel Corona virus first identified in December of 2019 (COVID-19) has evolved into a global pandemic resulting in countless deaths and impacting the global healthcare system severely. One of the many sequelae associated with COVID-19 is acute kidney injury (AKI). Rapidly evolving data has shown that AKI occurs in over half of critically ill COVID-19 patients.

The ADQI panel consists of experts in nephrology and critical care from around the world. This latest convention of the group met with the purpose of providing consensus positions on COVID-19 and AKI, using the recognized ADQI methodology and format. These statements center around recommendations for diagnosis, prevention and management of COVID-19 AKI and areas identified for future research.

The consensus statements included positions on the pathophysiology, epidemiology and clinical course of COVID-19-associated AKI, as well as prevention and management strategies, Renal Replacement Therapy (RRT), optimized anticoagulation strategies and use of extracorporeal blood purification (EBP) techniques.

DIAGNOSIS

Specifically regarding the diagnosis of COVID-19-associated AKI (COVID-19 AKI), the Consensus Statement recommends use of the Kidney Disease: Improving Global Outcomes (KDIGO) consensus definition for AKI. This includes the use of serum creatinine level and urine output in clinical practice, as well as kidney-specific tests and measures of kidney function to characterize clinical presentations, course and outcomes of AKI.

The Statement reported several studies in which urinalysis and biomarkers of AKI were frequently found to be abnormal in COVID-19 patients and could therefore be useful to characterize AKI in such patients.

It was also observed that patients with COVID-19 AKI and high levels of urinary biomarkers [TIMP-2•IGFBP-7], were more likely to progress to RRT than patients with AKI but with low [TIMP-2•IGFBP-7]. Furthermore, higher levels of systemic markers of inflammation, particularly ferritin, C-reactive protein, procalcitonin and lactate dehydrogenase, have been reported in patients with COVID-19 AKI.

CLINICAL COURSE AND PROGNOSIS

Further study of the mechanism, timing and clinical implications of traditional markers of AKI (proteinuria and haematuria) as well as novel biomarkers for the diagnosis and prognosis of AKI is needed.

CONCLUSIONS

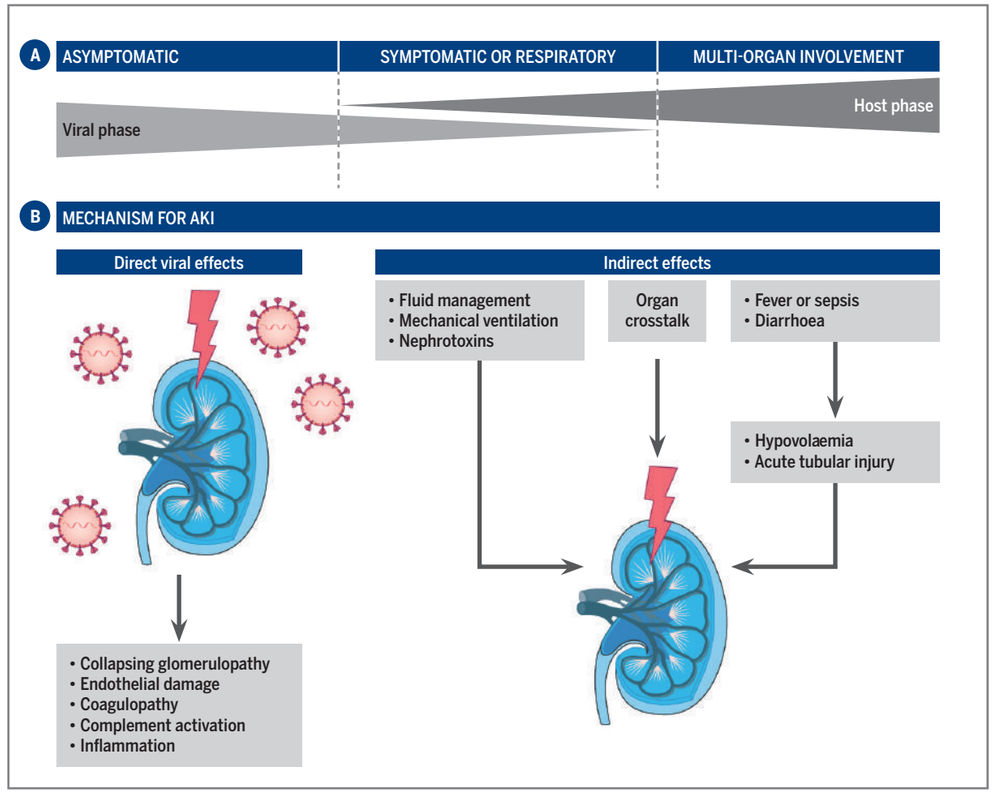
COVID-19 AKI is more common than initially thought and is associated with high mortality. Although rates of COVID-19 AKI vary considerably between studies and regions, an incidence of over 20% in hospitalized patients is widely observed. The pathogenesis of AKI in patients with COVID-19-AKI is likely multifactorial. Given that the risk factors, mechanisms and patient outcomes are similar between COVID-19 AKI and AKI of non-viral origin in the ICU, the treatment recommendations and preventative measures proposed in this Consensus Statement are therefore frequently common to both.

"Patients with COVID-19 AKI and high levels of tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein-7 [TIMP-2•IGFBP-7] were more likely to progress to RRT than patients with AKI but with low [TIMP-2•IGFBP-7]."

KEY FINDINGS

- AKI is now a recognized complication of SARS-CoV-2 infection.
- COVID-19 AKI is associated with adverse outcomes and a greater use of healthcare resources.
- Consensus recommends using KDIGO criteria for diagnosing and staging AKI in practice.
- Use of traditional markers and novel biomarkers are recommended in clinical practice to characterize clinical presentations, course and outcomes of AKI, as per KDIGO consensus definition.

Figure 1. Pathogenesis of COVID-19 AKI*.
Adaped from Nadim M, et al. *Nature Reviews Nephrology* 2020;16(12):747-764



*The pathogenesis of AKI in patients with COVID-19-AKI is likely multifactorial, involving both the direct effects of SARS-CoV-2 virus on the kidney and the indirect mechanisms resulting from systemic consequences of viral infection or effects of the virus on distant organs including the lung, in addition to mechanisms relating to the management of COVID-19.

REFERENCES

1. Zuk A, Bonventre JV. *Annual review of medicine* 2016; 67:293-307

2. Hoste EAJ, Bagshaw SM, Bellomo R, et al. **Epidemiology of acute kidney injury in critically ill patients.** *Intensive Care Medicine.* 2015; 41:1411-1423

3. Hoste EAJ, Lameire NH, Vanholder RC, et al. **Acute Renal Failure in Patients with Sepsis in a Surgical ICU: Predictive Factors, Incidence, Comorbidity, and Outcome.** *The Journal of the American Society of Nephrology* 2003;14:1022-1030

4. Bagshaw SM, George C, Bellomo R, et al. **Early acute kidney injury and sepsis: a multicentre evaluation.** *Critical Care* 2008;12(2):1

5. Martensson J, Martling CR, Bell M, et al. **Novel Biomarkers of Acute Kidney Injury and Failure: Clinical Applicability.** *British Journal of Anaesthesia* 2012;109(6):843-50

6. Wlodzimirow KA, Abu-Hanna A, Slabbekoorn M, et al. **A comparison of RIFLE with and without urine output criteria for acute kidney injury in critically ill patients.** *Critical Care* 2012;16:R200

7. Hobson C, Ozrazgat-Baslanti T, Kuxhausen A, et al. **Cost and mortality associated with postoperative acute kidney injury.** *Annals of Surgery* 2015;261:1207-1214

8. Hoste EAJ, Kellum JA, Selby NM, et al. **Global epidemiology and outcomes of acute kidney injury**. *Nature Reviews Nephrology* 2018;14(10):607-25

9. Mehta RL, Cerdá J, Burdmann EA, et al. **International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology**. *Lancet* 2015;385(9987):2616-43

10. Ostermann M, Cerdá J. **The Burden of Acute Kidney Injury and Related Financial Issues**. *Contributions to Nephrology* 2018;193:100-12

11. Varrier M, Forni LG, Ostermann M. **Long-term sequelae from acute kidney injury: potential mechanisms for the observed poor renal outcomes**. *Critical Care* 2015;19(1):102

12. Chawla LS, Bellomo R, Bihorac A, et al. **Acute kidney disease and renal recovery: consensus report of the Acute Disease Quality Initiative (ADQI) 16 Workgroup**. *Nature Reviews Nephrology* 2017;13(4):241-57

13. Kerr M, Bedford M, Matthews B, O'Donoghue D. **The economic impact of acute kidney injury in England**. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association*. 2014;29(7):1362-8

14. Kashani K, Al-Khafaji A, Ardiles T, et al. **Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury**. *Critical Care* 2013;17(1):R25

15. Meersch M, Schmidt C, Hoffmeier A, et al. **Prevention of cardiac surgery-associated AKI by implementing the KDIGO guidelines in high risk patients identified by biomarkers: the PrevAKI randomized controlled trial**. *Intensive Care Medicine* 2017;43(11):1551-6

16. Göcze I, Jauch D, Götz M, et al. **Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study**. *Annals of Surgery* 2018;267(6):1013-20

17. Engelman DT, Crisafi C, Germain M, et al. **Using urinary biomarkers to reduce acute kidney injury following cardiac surgery.** *The Journal of Thoracic and Cardiovascular Surgery* 2020;160(5):1235-46.e2

18. Joannidis M, Forni LG, Haase M, et al. **Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury**. *Critical Care Medicine* 2019;47(10):e820-e6

19. McCullough PA, Ostermann M, Forni LG, et al. **Serial Urinary Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 and the Prognosis for Acute Kidney Injury over the Course of Critical Illness**. *Cardiorenal Medicine* 2019;9(6):358-69

20. Ostermann M, McCullough PA, Forni LG, et al. **Kinetics of Urinary Cell Cycle Arrest Markers for Acute Kidney Injury Following Exposure to Potential Renal Insults**. *Critical Care Medicine* 2018;46(3):375-83

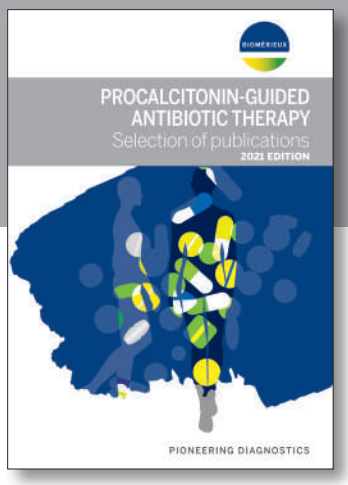
21. Ostermann M, Zarbock A, Goldstein S, et al. **Recommendations on Acute Kidney Injury Biomarkers From the Acute Disease Quality Initiative Consensus Conference: A Consensus Statement**. *JAMA Network Open* 2020;3(10):e2019209

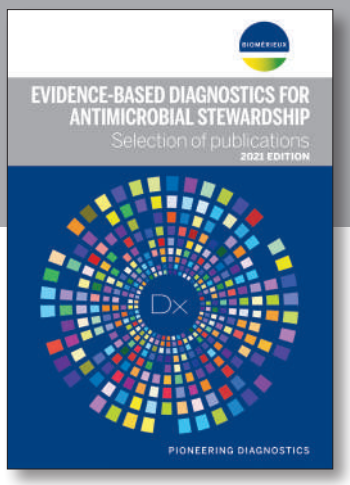
NOTES

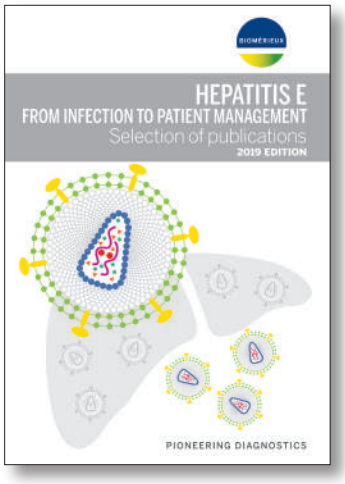
NOTES

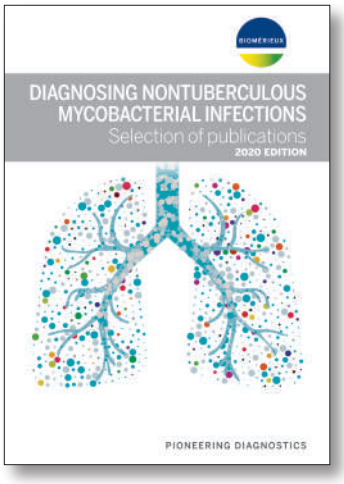
Other “Selection of publications” available

Contact your local bioMérieux representative to find out more about available literature









bioMérieux S.A. • 69280 Marcy l’Etoile • France • Tel.: + 33 (0)4 78 87 20 00 • Fax: +33 (0)4 78 87 20 90
www.biomerieux.com **www.biomerieux.com/en/education**