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Prognostic value of postoperative high-sensitivity troponin T in patients with different stages of kidney disease undergoing noncardiac surgery

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Abstract

Background: Emerging evidence suggests that postoperative troponin release is a strong and independent predictor of short-term mortality. However, evaluating elevated troponins in patients with chronic kidney disease (CKD) is still controversial and is often disregarded. This study examines morbidity along with short- and long-term mortality risk associated with elevated high-sensitivity troponin T (hsTnT) in patients with different stages CKD undergoing noncardiac surgery.
Methods: This observational cohort comprised 3262 patients aged ≥60 yr who underwent noncardiac surgery. Postoperative hsTnT concentrations were divided into normal [<14 ng l^{-1} (reference)], low (14–49 ng l^{-1}), moderate (50–149 ng l^{-1}), and high (≥150 ng l^{-1}) groups. A threshold of 50 ng l^{-1} was used to dichotomize hsTnT. The study endpoints were 30-day and long-term all-cause mortality, and postoperative myocardial infarction.
Results: Postoperative hsTnT was associated with a stepwise increase in 30-day and long-term mortality risk: low hsTnT adjusted hazard ratio (HR) 1.4 [95% confidence interval (CI): 1.1–1.7], moderate hsTnT adjusted HR 3.1 (95% CI: 2.3–4.3), high hsTnT adjusted HR 5.5 (95% CI: 3.6–8.4). Postoperative hsTnT ≥50 ng l^{-1} was associated with 30-day and long-term mortality risk for each stage of CKD. Elevated troponin concentrations in severe CKD (estimated glomerular filtration rate <30 mL min^{-1} 1.73 m^{-2}), however, did not predict short-term death.
Conclusions: Elevated postoperative hsTnT is associated with a dose-dependent increase in 30-day and long-term mortality risk in each stage of CKD with an estimated glomerular filtration rate ≥30 ml min^{-1} 1.73 m^{-2}.

Key words: chronic; mortality; renal insufficiency; surgery; troponin T

Mortality after noncardiac surgery is a major postoperative complication,[1] with myocardial infarction (MI) presumed to be one of the leading causes.[2 3] Recent studies have demonstrated postoperative troponin release, as a marker of subclinical myocardial injury, to be an independent predictor of short-term mortality in patients undergoing noncardiac surgery.[4–8] Because of its strong prognostic value, some argue for routine postoperative troponin measurements after noncardiac surgery.[8–10] The recent availability of a high sensitive troponin T (hsTnT) assay, with its superior diagnostic accuracy,[11] suggests hsTnT might have greater prognostic value in the perioperative setting.

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Editor's key points

- A fifth generation high-sensitivity troponin T (hsTnT) assay is now available
- Troponin elevation is mostly ascribed to myocardial injury, but poor kidney function can impair clearance
- This study found that elevated postoperative hsTnT concentrations, and myocardial infarction, were more common in patients with greater degrees of chronic kidney disease
- Higher postoperative hsTnT concentrations were associated with increased short- and long-term mortality in each stage of chronic kidney disease

Patients with chronic kidney disease (CKD) are known to have frequently asymptomatic elevated cardiac biomarkers,[12–14] making interpretation of these markers difficult.[13] Despite having a high risk of cardiovascular and postoperative mortality,[15 16] these markers are often disregarded as falsely elevated due to decreased renal clearance. Studies have however demonstrated elevated troponin concentrations in patients with an estimated glomerular filtration rate (eGFR) <60 ml min^{-1} 1.73 m^{-2} to be associated with a worse outcome.[17–19] It is reasonable that these elevations in asymptomatic patients with CKD are a true representation of subclinical myocardial injury rather than a consequence of decreased renal clearance and should not be disregarded.

In this study we aimed to examine the prognostic value of postoperative high-sensitivity troponin T (hsTnT) release in patients with different stages of CKD undergoing intermediate- and high-risk noncardiac surgery, evaluating the risk of short- and long-term mortality. We hypothesized that elevated postoperative hsTnT release would be associated with increased risk of mortality, irrespective of the different stages of CKD.

Methods

This observational cohort study was derived from an ongoing routine troponin registry of consecutive noncardiac surgery patients at the Erasmus University Medical Centre, Rotterdam, The Netherlands. The hospital has incorporated postoperative troponin assessment on a standard clinical basis since July 1, 2012. Eligibility criteria are patients undergoing intermediate- or high-risk non-cardiac surgery,[20 21] including elective and emergency surgery, an expected postoperative length of hospitalization of at least 24 h and an age of 60 yr or older. The study sample in the period from July 1, 2012 until December 31, 2015 was selected for current analysis. Patients were excluded if postoperative hsTnT concentrations or preoperative kidney function within 6 months prior to surgery were not available. In addition, kidney transplantation procedures and patients with end stage renal disease (ESRD)[22] were excluded due to expected instability in perioperative renal function and survival.[13 23] institutional approval for this study was obtained. This study was not subject to the Dutch Medical Research Involving Human Subjects Act[24] due to this observational character and complies with the Helsinki Declaration on research ethics.[25] This report follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for observational trials.[26]

Baseline characteristics

Before surgery, patients' details were obtained during preoperative evaluation. Patients were screened on medical history, physical examination, laboratory measurements, and an electrocardiogram according to local policy. Baseline characteristics were acquired from medical records, and consisted of age, sex, type of surgery (orthopaedic, general, urological or gynaecological, vascular, or other), emergency procedures, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, prior MI, coronary artery disease, congestive heart failure, cerebrovascular disease, and peripheral artery disease. For all patients, a cardiac risk score was determined applying the Revised Cardiac Risk Index.[27] Additionally, preoperative use of medication was recorded, including β-blockers, statins, aspirin, oral anticoagulants, angiotensin-converting enzyme inhibitors, angiotensin-II antagonists, and diuretics.

Renal function

Before surgery, serum creatinine concentration assessment was obtained to estimate preoperative GFR. Renal function was estimated by use of the simplified Modification of Diet in Renal Disease prediction equation[28] defined as:

$$\text{eGFR} = 186.3 \times (\text{serum creatinine})^{-1.154} \times \text{age}^{-0.203} \times (0.742 \text{ for women}). \quad (1)$$

Renal function was categorized using the Kidney Disease Quality Outcome Initiative guidelines (K/DOQI).[22] According to the K/DOQI guidelines stage 1 of CKD represents a normal kidney function (eGFR ≥90 ml min^{-1} 1.73 m^{-2}) and stage 2 a mildly reduced kidney function (eGFR 60–89 ml min^{-1} 1.73 m^{-2}) if there is other evidence of kidney disease. Due to estimation of the equation being inaccurate at eGFR ≥60 ml min^{-1} 1.73 m^{-2},[29] stages 1 and 2 were combined in the study representing normal kidney function (eGFR ≥60 ml min^{-1} 1.73 m^{-2}). CKD with moderate reduction in glomerular filtration was defined as eGFR between 30–59 ml min^{-1} 1.73 m^{-2} including subclassifications 3a (eGFR 45–59 ml min^{-1} 1.73 m^{-2}) and 3b (eGFR 30–44 ml min^{-1} 1.73 m^{-2}).[30] CKD with severe glomerular filtration reduction was defined as eGFR <30 ml min^{-1} 1.73 m^{-2}, in which stages 4 (eGFR 15–29 ml min^{-1} 1.73 m^{-2}) and 5 (eGFR <15 ml min^{-1} 1.73 m^{-2}) were combined considering the small number of subjects in both groups.

Troponin measurements

Routine hsTnT measurements were obtained on postoperative days 1, 2, and 3, unless discharged earlier, or when clinically indicated. The hsTnT measurements were done using the Cobas e602 Troponin T hs STAT assay from Roche Diagnostics, Mannheim, Germany. Peak hsTnT measurement during the first 3 postoperative days was recorded for analysis.

The hsTnT thresholds were based on the manufacturer's and previous determined postoperative prognostic values of the fourth generation assay.[7] The lowest threshold was the manufacturer's 99th percentile of a normal population, i.e. 14 ng l^{-1}.[31] The second was based on the 0.03 ng ml^{-1} threshold of the fourth generation assay's abnormal elevations, which is equivalent to 50 ng l^{-1} of the fifth assay.[31] The highest threshold was extrapolated from the highest threshold in the

Vascular Events In Noncardiac Surgery Patients Cohort Evaluation (VISION) study,[7] which was 10 times the threshold of an abnormal troponin elevations, i.e. 140 ng l^{-1} for the 5th generation, rounding off to 150 ng l^{-1}.

Subsequently a normal hsTnT concentration was defined as a peak hsTnT concentration below the 99th percentile (<14 ng l^{-1}). A peak hsTnT between 14–49 ng l^{-1} was defined as low hsTnT concentrations, a peak between 50–149 ng l^{-1} as moderate hsTnT concentrations and a peak ≥150 ng l^{-1} as high hsTnT concentrations. Finally, a peak hsTnT concentrations ≥50 ng l^{-1} was used for dichotomization based on the fourth generation cut-off value of myocardial injury after noncardiac surgery as a perioperative outcome.[32]

Study endpoints

Median follow-up duration was 2.1 yr (interquartile range 1.5–2.8 yr). The primary study endpoint was 30-day mortality after surgery and long-term mortality as the secondary endpoint. Survival status was completed in all patients by means of using the institution's medical records or was ascertained by inquiry from the civil registries. A total of 19 patients (0.6%) had emigrated, the date of emigration was recorded and patients were censored at this date or the last date from the hospital records for analysis due to loss to follow-up.

In our *post hoc* analysis, postoperative MI, based on the third universal definition,[33] was assessed after surgery and was further explored as a secondary endpoint.

Statistical analysis

Continuous variables are presented as medians with interquartile range and categorical variables are presented as *n* (%). Continuous data were compared using the Kruskal–Wallis test and categorical data were compared using the χ^2 test. Using the Kaplan–Meier method, cumulative long-term survival was determined and differences between group survival distributions were compared with the log-rank test. Binominal logistic regression and Cox proportional hazards models were used to evaluate the 30-day and long-term mortality risk of hsTnT concentrations and for the different stages of CKD. The assumption of proportional hazards was verified by assessing correlations using Pearson correlation tests, between Schoenfeld residuals of all covariates and ranked survival time. If covariates violated the proportional hazards-assumption, the model was extended by creating a time-dependent variable (i.e. the covariate in question multiplied by time) and adding them to the final model. Normal kidney function and a normal hsTnT were used as the reference groups for the different stages of CKD and postoperative peak hsTnT concentrations, respectively. The interaction between stages of CKD, postoperative hsTnT, and emergency procedures were tested and dropped if not significant. Positive likelihood ratios for postoperative myocardial infarction were calculated manually. Logistic and Cox regression analyses were adjusted for selected covariates. Selection of the potential confounders was based on former epidemiological research known factors associated with postoperative myocardial injury,[7 9] perioperative cardiovascular and/or mortality risk.[20 27] We entered all variables in the model to give an as unbiased as possible estimate for the association between hsTnT, eGFR, and mortality. Multivariate analyses were repeated after stratifying for each group of CKD. Sensitivity analyses were performed by repeating multivariable logistic and Cox regression analyses to determine the influence of emergency procedures on 30-day and long-term mortality. Sensitivity analyses were repeated for the cohort before and after the implementation of electronic laboratory ordering to account for the missing postoperative troponins in the former.

Results are reported as either odds ratios or hazard ratios (HRs) with their 95% confidence intervals. Significance was set at $P<0.05$ for main effects and interaction terms. All statistical analyses were performed using IBM SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

The study cohort consisted of 4825 consecutive noncardiac surgery patients who underwent elective and emergency surgery (Fig. 1). In 1287 (27%) patients' postoperative hsTnT was unavailable, in 31 the preoperative kidney function was missing, 47 had preoperative laboratory results older than 6 months, 171 of the operations were kidney transplantation procedures (comprised of pre- or ESRD patients) and 27 patients had ESRD, which were all excluded. Subsequently, the final study sample included a total of 3262 patients; 2394 (73%) had normal kidney function, 541 (17%) moderate 3a CKD, 217 (7%) moderate 3b CKD, and 110 (3%) severe CKD.

Baseline characteristics

Baseline characteristics of the final study sample are presented in Table 1. Cardiovascular risk profile showed a significant inverse relationship with kidney function, i.e. the prevalence being more common in patients with severe CKD opposed to the other stages of CKD: hypertension, diabetes mellitus, prior history of MI, coronary artery disease, congestive heart failure, cerebrovascular disease, and peripheral artery disease ($P<0.01$ for all). Furthermore, the use of aspirin, oral anticoagulants, β-blockers, angiotensin-converting enzyme inhibitors, angiotensin II antagonists, diuretics, and statins was more frequent in patients with reduced kidney function ($P< 0.01$).

Postoperative hsTnT concentrations had an inverse relationship with kidney function with median peak hsTnT concentrations lowest in the patients with normal kidney function and highest in patients with severe CKD (13–53 ng l^{-1}, $P<0.01$; Table 2). The majority (55%) of the patients with normal kidney function had a normal hsTnT concentration (<14 ng l^{-1}), while this percentage decreased to 6% in the severe CKD group ($P<0.01$).

Study endpoints

A total of 91 (3%) patients sustained a postoperative MI, 115 (4%) died during the 30-day follow-up and a total of 505 (16%) died during the long-term follow-up. The incidence of postoperative MI, 30-day and long-term mortality increased with increasing postoperative hsTnT concentrations, respectively (Table 3). A similar trend is shown in the increasing severity of CKD. This stepwise relation of hsTnT with mortality was prevalent in all stages of CKD, both for 30-day as well as long-term mortality. Moreover, the positive likelihood ratio of diagnosing a MI when patients had hsTnT ≥50 ng l^{-1} decreased with increasing severity of CKD: normal kidney function LHR+=17.7, moderate 3a CKD LHR+=11.2, moderate 3b CKD LHR+=4.1, and severe CKD LHR+=2.1.

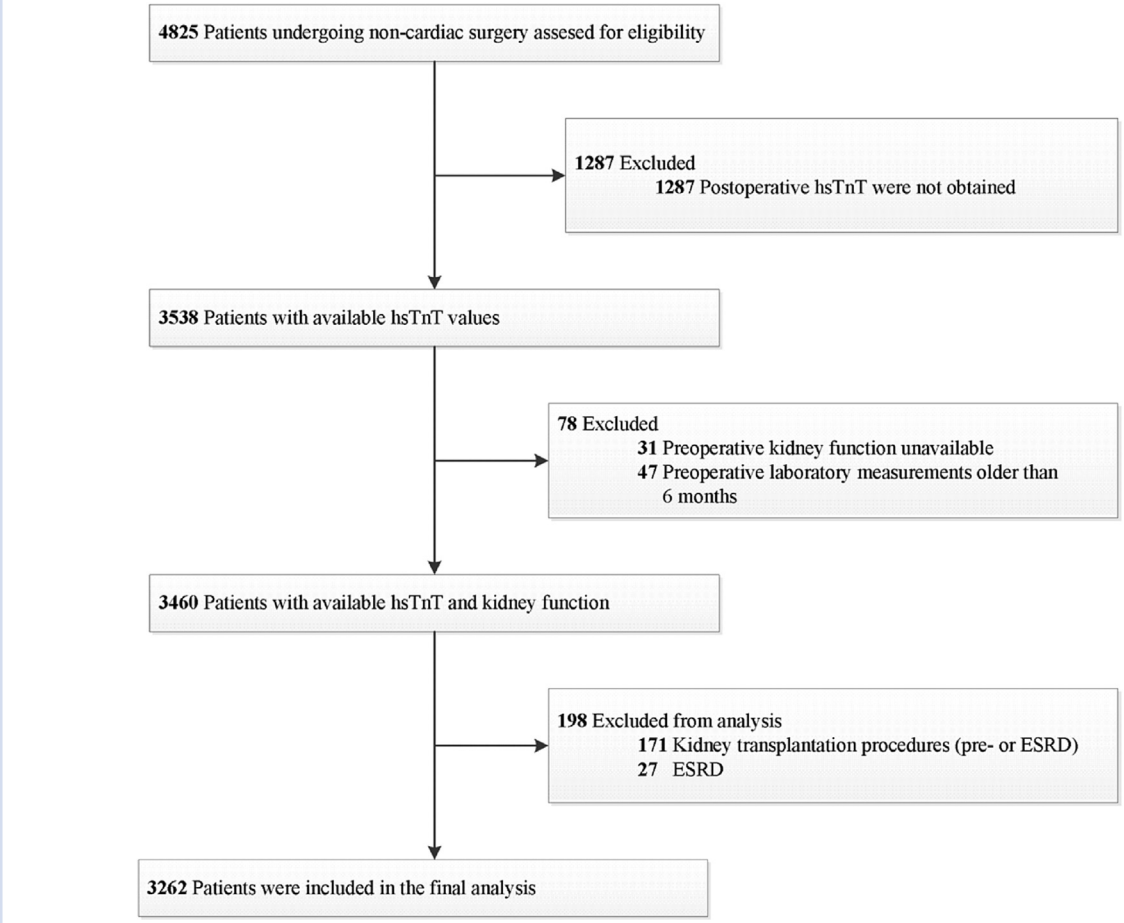

Fig 1. Patient flow chart. ESRD, end-stage renal disease; hsTNT, high-sensitivity troponin T.

Additionally, adjusted logistic regression and Cox proportional hazard models for 30-day and long-term mortality revealed the same association; a stepwise increase in risk according to each increase of postoperative hsTnT elevation (Table 4). There was no significant interaction between stages of CKD and postoperative hsTnT in the models. A significant time-dependency effect for emergency procedures and hsTnT was observed in the long-term mortality model (Supplementary Table 1). After stratifying for the stages of CKD, cumulative survival between different concentrations of postoperative hsTnT was comparable in each stage of CKD (Fig. 2). A log-rank test confirmed differences in survival between hsTnT concentrations ($P<0.05$ within each stage of CKD). After dichotomizing hsTnT and repeating multivariate models within each strata of CKD, peak hsTnT $\geq$50 ng l^{-1} did not significantly predict short-term death in severe CKD (Fig. 3). Our principal findings remained similar after excluding emergency procedures.

Discussion

In the present study, we investigated the prognostic value of postoperative hsTnT release in patients with different stages of CKD undergoing intermediate- and high-risk noncardiac surgery, evaluating the risk of short- and long-term mortality. We found higher incidence of elevated postoperative hsTnT concentrations, and MI was more common in patients, with greater CKD. After adjustment for comorbidities, higher concentrations of postoperative hsTnT coincided with increased risk of 30-day and long-term mortality in each group of CKD with an eGFR $\geq$30 ml min^{-1} 1.73 m^{-2}. Although the incidence of postoperative MI was higher in severe CKD, a higher hsTnT was not necessarily associated with an MI (i.e. masking the MI). Furthermore, after stratifying for the different stages of CKD, postoperative concentrations of hsTnT displayed similar patterns in cumulative survival.

Our findings of increased 30-day and long-term mortality according to postoperative troponins after noncardiac surgery is consistent with earlier studies using the fourth generation troponin T assay.[4 7 8 34] Recently the VISION investigators presented comparable associations using the fifth generation's hsTnT assay in a large international cohort, determining prognostically relevant thresholds via an iterative process.[35] Their calculated thresholds (20, 65, and 1000 ng l^{-1}, respectively) demonstrated a similar stepwise increase of 30-day mortality risk. Additionally, they found no interaction between eGFR and postoperative hsTnT.

Table 1 Baseline characteristics of patients according to stages of kidney disease. ACE, angiotensin converting enzyme, COPD, chronic obstructive pulmonary disease; IQR, interquartile range

	eGFR (ml min^{-1} 1.73 m^{-2})				
	≥60 (*n*=2394)	45–59 (*n*=541)	30–44 (*n*=217)	<30 (*n*=110)	*P*
Patient characteristics					
Age (yr), median (IQR)	69 (65–74)	73 (68–78)	74 (68–80)	72 (65–77)	<0.001
Male, n (%)	1408 (58.8)	299 (55.3)	127 (58.5)	70 (63.6)	0.309
Type of surgery – *n* (%)					<0.001
Orthopaedic	329 (13.7)	77 (14.2)	19 (8.8)	6 (5.5)	
General	399 (16.7)	81 (15.0)	30 (13.8)	5 (4.5)	
Urologic or gynaecologic	383 (16.0)	92 (17.0)	38 (17.5)	24 (21.8)	
Vascular	571 (23.9)	165 (30.5)	86 (39.6)	54 (49.1)	
Other	712 (29.7)	126 (23.3)	44 (20.3)	21 (19.1)	
Emergency procedures – *n* (%)	124 (5.2)	41 (7.6)	27 (12.4)	20 (18.2)	<0.001
Medical history – *n* (%)					
Hypertension	1150 (48.0)	357 (66.0)	156 (71.9)	79 (71.8)	<0.001
Diabetes mellitus	488 (20.4)	135 (25.0)	74 (34.1)	46 (41.8)	<0.001
COPD	319 (13.3)	84 (15.5)	40 (18.4)	19 (17.3)	0.096
Myocardial infarction	226 (9.4)	86 (15.9)	45 (20.7)	30 (27.3)	<0.001
Coronary artery disease	329 (13.7)	109 (20.1)	64 (29.5)	40 (36.4)	<0.001
Congestive heart failure	79 (3.3)	44 (8.1)	32 (14.7)	26 (23.9)	<0.001
Cerebrovascular disease	325 (13.6)	115 (21.3)	52 (24.0)	28 (25.5)	<0.001
Peripheral artery disease	230 (9.6)	73 (13.5)	44 (20.3)	22 (20.0)	<0.001
Revised Cardiac Risk Index					<0.001
0 risk factors	1167 (48.7)	209 (38.6)	49 (22.6)	5 (4.5)	
1 risk factor	804 (33.6)	173 (32.0)	75 (34.6)	17 (15.5)	
2 risk factors	309 (12.9)	97 (17.9)	44 (20.3)	24 (21.8)	
≥3 risk factors	114 (4.8)	62 (11.5)	49 (22.6)	64 (58.2)	
Medication use – *n* (%)					
Aspirin	684 (28.6)	187 (34.6)	86 (39.6)	50 (45.5)	<0.001
Oral anticoagulants	232 (9.7)	85 (15.7)	57 (26.3)	28 (25.5)	<0.001
Beta-blockers	733 (30.6)	244 (45.1)	128 (59.0)	61 (55.5)	<0.001
ACE-inhibitors	521 (21.8)	139 (25.7)	67 (30.9)	34 (30.9)	0.001
Angiotensin II antagonists	366 (15.3)	135 (25.0)	62 (28.6)	29 (26.4)	<0.001
Diuretics	561 (23.4)	196 (36.2)	103 (47.5)	60 (54.5)	<0.001
Statins	952 (39.8)	255 (47.1)	120 (55.3)	77 (70.0)	<0.001

Table 2 Postoperative hsTnT release according to stages of kidney disease. IQR, interquartile range

	eGFR (ml min–1 1.73 m–2) CKD				*P*
	≥60 Normal	45–59 Moderate 3a	30–44 Moderate 3b	<30 Severe	
hsTnT release					
Peak hsTnT – median (IQR)	12.9 (8.6–20.4)	17.5 (11.9–28.4)	28.8 (17.5–51.8)	53.0 (25.4–89.4)	<0.001
hsTnT groups – *n* (%)					<0.001
<14 ng l^{-1}	1309 (54.7)	191 (35.3)	32 (14.7)	7 (6.4)	
14-49 ng l^{-1}	913 (38.1)	289 (53.4)	129 (59.4)	46 (41.8)	
50-149 ng l^{-1}	123 (5.1)	43 (7.9)	45 (20.7)	40 (36.4)	
≥150 ng l^{-1}	49 (2.0)	18 (3.3)	11 (5.1)	17 (15.5)	
hsTnT ≥50 ng l^{-1} -*n* (%)	172 (7.2)	61 (11.3)	56 (25.8)	**57 (51.8)**	<0.001

The study by Walsh and colleagues[36] displays the same increased risk of 30-day all-cause mortality between the different strata of CKD when postoperative troponin T was elevated (≥0.02 ng ml^{-1} fourth generation assay) up to CKD with an eGFR ≥30 ml min^{-1} 1.73 m^{-2}. Our study confirmed similar results in patients with CKD using the fifth generation hsTnT assay and furthermore demonstrates an increased risk of long-term mortality, which was unclear in patients with severe CKD. Similar to Walsh and colleagues,[36] patients with severe CKD in our cohort were more subject to undergo emergency procedures. Observing the same trend in a larger cohort than ours, suggests that this is a selection bias for which we cannot fully adjust. Additionally to mortality, other studies demonstrated troponins to be a predictor of adverse cardiovascular outcome in patients with CKD.[14 29 37 38]

Physicians generally find it challenging to evaluate troponins in patients with CKD. Patients with CKD are commonly presented with elevated troponin concentrations at baseline,[12] which makes it difficult to distinguish if they are at risk when they are asymptomatic. Additionally, with the use of the highly sensitive troponin T assay, studies report the majority of patients with CKD to frequently present with elevated

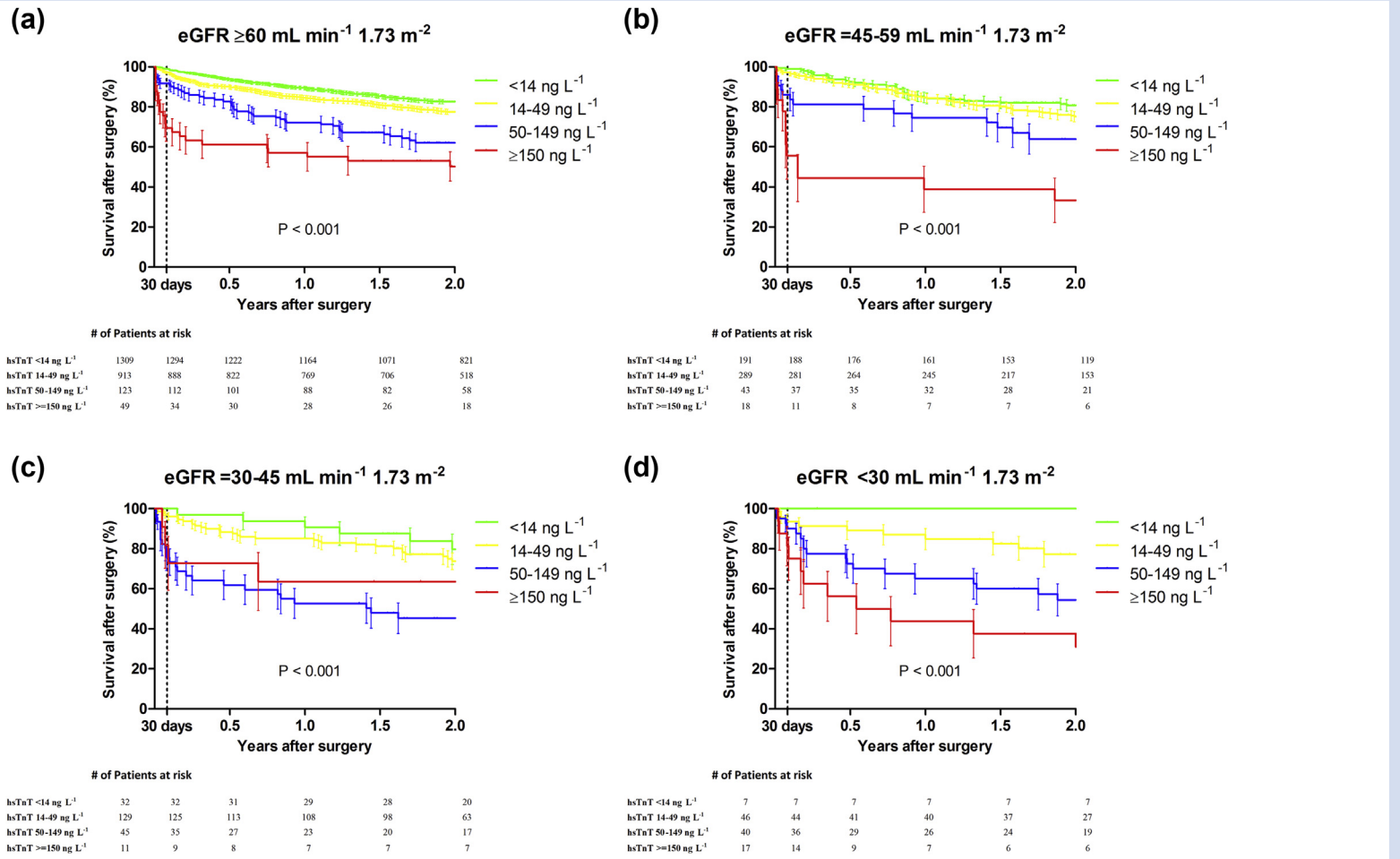

Fig 2. The cumulative survival of postoperative all-cause mortality in patients with different stages of kidney disease. (a) Normal kidney function; (b) Moderate CKD 3a; (c) Moderate CKD 3b; (d) Severe CKD. Survival curves are plotted with standard error bars. CKD, chronic kidney disease.

Table 3 Postoperative myocardial infarction, 30-day and 1-year all-cause mortality according to stages of kidney disease and postoperative hsTnT

	eGFR (ml min^{-1} 1.73 m^{-2})				Total (n=3262)
	≥60 (n=2394)	45–59 (n=541)	30–44 (n=217)	<30 (n=110)	
Myocardial infarction (%)	48/2394 (2.0)	18/541 (3.3)	15/217 (6.9)	10/110 (9.1)	91/3262 (2.8)
Peak hsTnT (ng l^{-1})					
<14 (n=1539)	0/1309 (0.0)	1/191 (0.5)	0/32 (0.0)	0/7 (0.0)	1/1539 (0.1)
14-49 (n=1377)	2/913 (0.2)	0/289 (0.0)	2/129 (1.6)	0/46 (0.0)	4/1377 (0.3)
50-149 (n=251)	23/123 (18.7)	5/43 (11.6)	6/45 (13.3)	5/40 (12.5)	39/251 (15.5)
≥150 (n=95)	23/49 (46.9)	12/18 (66.7)	7/11 (63.6)	5/17 (29.4)	47/95 (49.5)
≥50 (n=346)	46/172 (26.7)	17/61 (27.9)	13/56 (23.2)	10/57 (17.5)	86/346 (24.9)
30-day mortality (%)	65/2394 (2.7)	23/541 (4.3)	16/217 (7.4)	11/110 (10.0)	115/3262 (3.5)
Peak hsTnT (ng l^{-1})					
<14 (n=1539)	13/1309 (1.0)	2/191 (1.0)	0/32 (0.0)	0/7 (0.0)	15/1539 (1.0)
14–49 (n=1377)	26/913 (2.8)	8/289 (2.8)	4/129 (3.1)	3/47 (6.5)	41/1377 (3.0)
50–149 (n=251)	11/123 (8.9)	6/43 (14.0)	10/45 (22.2)	4/40 (10.0)	31/251 (12.4)
≥150 (n=95)	15/49 (30.6)	7/18 (38.9)	2/11 (18.2)	4/17 (23.5)	28/95 (29.5)
≥50 (n=346)	26/172 (15.1)	13/61 (21.3)	12/56 (21.4)	8/57 (14.0)	59/346 (17.1)
1-year mortality (%)	333/2394 (13.9)	95/541 (17.6)	47/217 (21.7)	30/110 (27.3)	505/3262 (15.5)
Peak hsTnT (ng l^{-1})					
<14 (n=1539)	136/1309 (10.4)	29/191 (15.2)	3/32 (9.4)	0/7 (0.0)	168/1539 (10.9)
14–49 (n=1377)	141/913 (15.4)	44/289 (15.2)	19/129 (14.7)	6/47 (13.0)	210/1377 (15.3)
50–149 (n=251)	35/123 (28.5)	11/43 (25.6)	21/45 (46.7)	14/40 (35.0)	81/251 (32.3)
≥150 (n=95)	21/49 (42.9)	11/18 (61.1)	4/11 (36.4)	10/17 (58.8)	46/95 (48.4)
≥50 (n=346)	56/172 (32.6)	22/61 (36.1)	25/56 (44.6)	24/57 (42.1)	127/346 (36.7)

Table 4 Thirty-day and long-term prognostic value of postoperative hsTnT and stages of kidney disease. *P values for interaction terms of kidney function and postoperative hsTnT were >0.05. †Adjusted for emergency procedures, history of hypertension, diabetes mellitus, COPD, coronary artery disease, congestive heart failure, cerebrovascular disease, and peripheral artery disease. ‡Adjusted for emergency procedures, history of hypertension, diabetes mellitus, COPD, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, time-dependent variable for hsTnT, emergency procedures, and interaction term between hsTnT and emergency procedures. ||Adjusted for emergency procedures, history of hypertension, diabetes mellitus, COPD, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, and interaction term between hsTnT and emergency procedures

	30-day mortality		Long-term mortality	
	Univariable OR	Multivariable aOR*,†	Univariable HR	Multivariable aHR*,‡
Peak hsTnT (ng l^{-1})				
<14	Reference		Reference	
14–49	3.1 (1.7–5.7)	2.8 (1.5–5.1)	1.4 (1.2–1.6)	1.4 (1.1–1.7)
50–149	14.3 (7.4–27.02)	10.2 (5.1–20.3)	3.1 (2.5–3.8)	3.1 (2.3–4.3)
≥150	42.5 (21.7–83.2)	26.6 (12.7–56.0)	4.9 (3.7–6.5)	5.5 (3.6–8.4)
eGFR (ml min^{-1} 1.73 m^{-2})				
≥60	Reference		Reference	
45–59	1.6 (0.9–2.6)	1.1 (0.6–1.8)	1.3 (1.1–1.6)	1.2 (1.0–1.4)
30–44	2.9 (1.6–5.0)	1.2 (0.6–2.3)	1.7 (1.4–2.2)	1.3 (1.0–1.7)
<30	4.0 (2.0–7.8)	0.8 (0.4–1.8)	2.5 (1.9–3.3)	1.4 (1.1–1.9)
	Univariable OR	Multivariable aOR*,‖	Univariable HR	Multivariable aHR*,‡
Peak hsTnT (ng l^{-1})				
<50	Reference		Reference	
≥50	10.5 (7.1–15.4)	10.6 (6.4–17.5)	2.9 (2.5–3.5)	3.2 (2.4–4.1)
eGFR (ml min^{-1} 1.73 m^{-2})				
≥60	Reference		Reference	
45–59	1.6 (0.9–2.5)	1.2 (0.7–2.0)	1.3 (1.1–1.6)	1.3 (1.0–1.5)
30–44	2.9 (1.6–5.0)	1.3 (0.7–2.4)	1.7 (1.4–2.2)	1.4 (1.1–1.8)
<30	4.0 (2.0–7.8)	0.9 (0.5–2.0)	2.5 (1.9–3.3)	1.5 (1.1–2.0)

hsTnT,[14 39] similar to our cohort (Table 2). The fifth generation hsTnT assay, however, uses the 99th percentile cut-off based on a healthy general population, which may not be proper for a subpopulation with persistent elevated troponins like CKD. Several studies have raised concerns regarding the diagnostic accuracy of hsTnT in patients with CKD for MI, due to varying estimates of sensitivity and specificity.[40] In our cohort, elevated troponin T concentrations in severe CKD were not

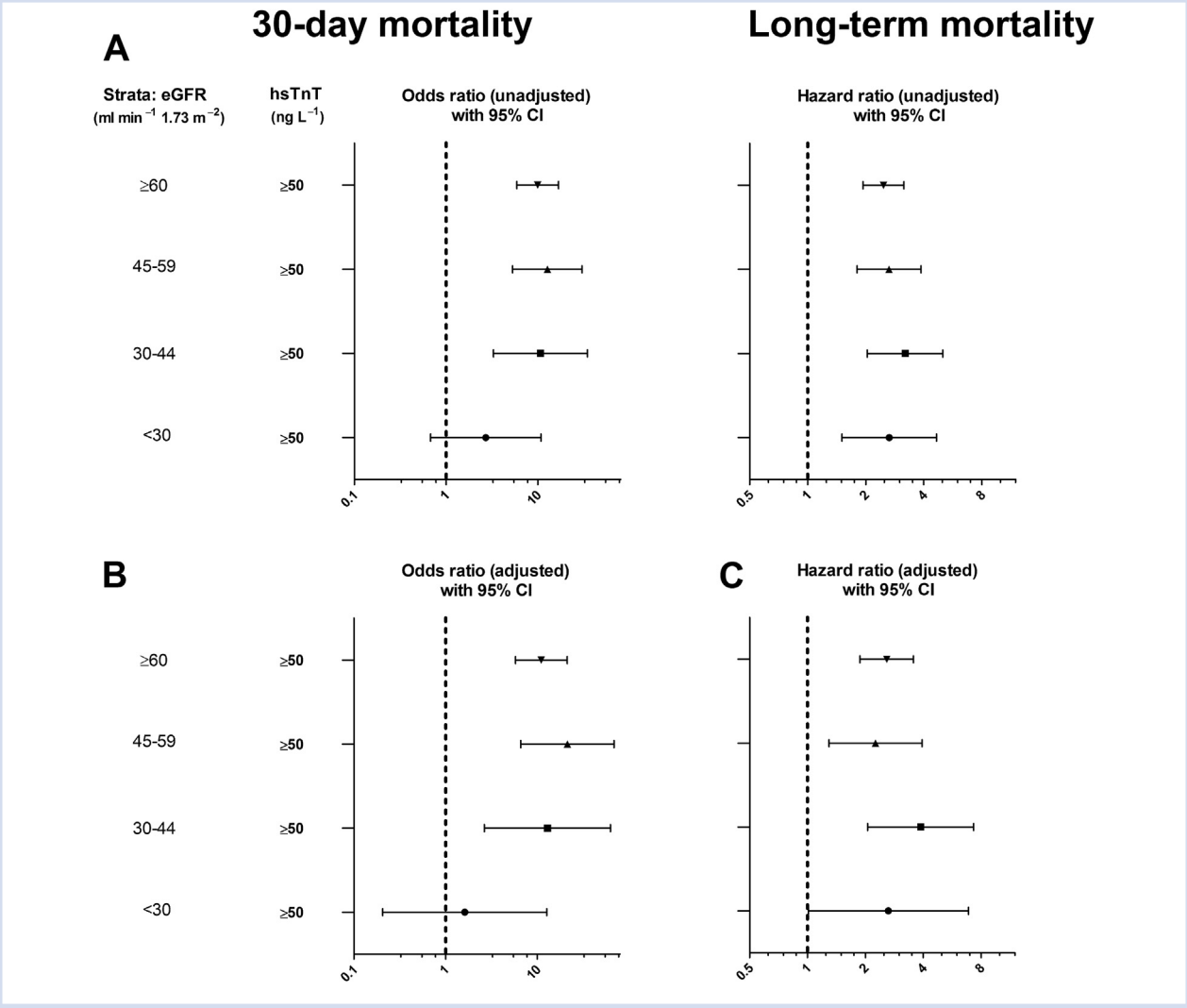

Fig 3. Forest plots of 30-day and long-term mortality risk. *P*-values of interaction terms between hsTnT and eGFR within a full multivariate model were >0.05. (A). Odds ratios, hazard ratios, and their respective confidence intervals (CIs) are shown of hsTnT ≥50 ng l^{-1} within each strata of CKD. (B) Adjusted for emergency procedures, history of hypertension, diabetes mellitus, COPD, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease and interaction term between hsTnT and emergency procedures. (C) Adjusted for emergency procedures, history of hypertension, diabetes mellitus, COPD, coronary artery disease, congestive heart failure, cerebrovascular disease, peripheral artery disease, time-dependent variable for hsTnT, emergency procedures, and interaction term between hsTnT and emergency procedures.

associated with detecting MI. However, diagnostic accuracy is increased in CKD if higher cut-off values are used and a subsequent hsTnT value is acquired to notice a change in troponin concentration.[41]

Although our study had limited power to determine whether elevated postoperative hsTnT predicts death in patients with severe CKD, other studies have found a higher risk of worse cardiovascular outcome and postoperative death.[15 16] Further research is needed to understand the underlying mechanism of myocardial injury in severe CKD to clarify how these specific cardiac biomarkers can aid in identifying high-risk asymptomatic patients.

In comparison with previous reports, our study confirms the same dose-dependent risk for concentrations of postoperative hsTnT in each different stage of CKD with an eGFR ≥30 ml min^{-1} 1.73 m^{-2}. Our study is the first to also investigate the long-term mortality risk in CKD patients undergoing noncardiac surgery along with using the fifth-generation troponin T assay.

Limitations

In the current study several limitations must be considered. Patients with severe CKD were more subject to undergo emergency procedures, which could have created an overestimation in mortality. Renal function was stratified on one individual measurement, not taking into account fluctuations in renal clearance in the perioperative period. Another limitation is the missing postoperative hsTnT, which mainly occurred before the implementation of electronic laboratory

orders in May 2014. Sensitivity analyses of the cohort before and after the implementation yielded similar results. Moreover, the incidence of different stages of CKD was the same in both cohorts.

Furthermore, our postoperative hsTnT cut-offs were based on thresholds of the fourth troponin T generation. Secondly, the IFCC recommends 99th percentile sex-specific cut-offs with the use of the fifth generation troponin T assay,[42] which we did not adjust for. There might be an underestimation of elevated troponins in females, as males have higher values. Third, a higher age influenced hsTnT and consequently our cohort since older men were more prevalent in worse CKD. Preoperative hsTnT measurements were mostly unavailable. Therefore, it was not possible to determine whether the patients already had pre-existing high concentrations of hsTnT, nor whether patients with CKD had a higher hsTnT steady state or suffered from myocardial injury during surgery. Nonetheless, the aim of our study was to investigate the predictive value of elevated postoperative hsTnT, regardless of the elevated hsTnT cause.

The sample size of patients in the lower CKD decreased the power after stratification. Finally, multivariate analyses of hsTnT categories on 30-day mortality should be interpreted with some caution due to the small number of events. We therefore included a model with dichotomized peak hsTnT as well, to be more conservative.

Conclusions

In this cohort of patients undergoing non-cardiac surgery, myocardial injury was common and higher postoperative hsTnT concentrations were associated with an increased short- and long-term mortality in each stage of CKD with an eGFR $\geq$30 ml min^{-1} 1.73 m^{-2}. While elevated concentrations of postoperative hsTnT was more common in patients with severe CKD, these elevations potentially mask the detection of postoperative MI. Interpretation of these elevations in severe CKD remains unclear and further research is warranted to be able to identify asymptomatic patients at high perioperative risk.

Authors' contributions

V.L. and S.H. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: F.v.L., V.L.
Acquisition, analysis, or interpretation of data: all authors.
Drafting of the manuscript: V.L., S.H., F.W., K.M., F.v.L.
Critical revision of the manuscript for important intellectual content: S.H., F.G., R.J.S, F.v.L.
Statistical analysis: V.L., S.H.
Administrative, technical, or material support: V.L., S.H., F.W., K.M., F.G.
Study supervision: S.H., F.v.L.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2017.09.003.

Declaration of interest

All authors declare that there are no conflicts of interest.

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