Authors' Response to Reviews of

Hospital Admission Risk Stratification of Patients with Gout presenting to the Emergency Department

Wang et al.
Clinical Rheumatology CLRH-D-21-00898.

RC: ***Reviewers' Comment***, AR: Authors' Response, ☐ Manuscript Text

Dear reviewers, many thanks for your valuable comments, which we feel add a lot of value to our manuscript.

1. Reviewer #1

RC: ***Why didn't you include hypertension and dyslipidemia in your analysis and in table 1? As you stated these are very common comorbidities in gout patients. Furthermore, why didn't you include the number of comorbidities in the model?***

AR: We thank the reviewer for the advice. We have now added hypertension and hyperlipidemia into our analysis, and both of them were significant in the univariable analysis. In multivariable analysis, while hyperlipidemia was no longer significant, hypertension remained significant and was included in the final model. We have modified multiple parts of the manuscript accordingly as follows.

Materials and Methods – Paragraph 2

Patient demographics (age, gender, ethnicity), chronic comorbidities including hypertension, hyperlipidemia and the ones in the Charlson Comorbidity Index [9], and their past medical resource utilisation prior to the ED visit were retrieved from the hospital's electronic medical records.
…

Results – Paragraph 2

Table 2 shows the output from the multivariable logistic regression model. Older age and presence of hypertension and chronic kidney disease were associated with higher odds of hospitalisation.
…

Discussion – Paragraph 2

As expected, our study demonstrated a significant burden of comorbidity in patients hospitalised for gout; 64.4%, 41.9%, 32.8%, 50.1% and 51.0% had hypertension, hyperlipidemia, cardiovascular disease, diabetes, and chronic kidney disease respectively.
…
The presence of hypertension especially was associated with 3.00 times higher odds of gout-related hospitalisation.
…

Table 1: Baseline characteristics of patients and comparison between those hospitalised vs discharged from the ED

Characteristics	Overall	Discharged	Hospitalised	p-Value
n (%)	1417	956 (67.5)	461 (32.5)	
Demographics				
Age (median [Q1, Q3])	56 [40, 70]	49 [35, 62]	70 [59, 78]	**<0.001**
Gender (male) (%)	1162 (82.0)	836 (87.4)	326 (70.7)	**<0.001**
Race (%)				**<0.001**
Chinese	759 (53.6)	485 (50.7)	274 (59.6)	
Malay	348 (24.6)	231 (24.2)	117 (25.4)	
Indian	110 (7.8)	79 (8.3)	31 (6.7)	
Others	200 (14.1)	161 (16.8)	39 (8.5)	
Comorbidities				
Hypertension (%)	463 (32.7)	166 (17.4)	297 (64.4)	**<0.001**
Hyperlipidemia (%)	303 (21.4)	110 (11.5)	193 (41.9)	**<0.001**
Cardiovascular Disease (%)	226 (15.9)	75 (7.8)	151 (32.8)	**<0.001**
Cancer (%)	50 (3.5)	17 (1.8)	33 (7.2)	**<0.001**
Diabetes (%)	392 (27.7)	160 (16.7)	231 (50.1)	**<0.001**
Chronic Kidney Disease (%)	354 (25.0)	118 (12.3)	235 (51.0)	**<0.001**
Others (%)	126 (8.9)	57 (6.0)	69 (15.0)	**<0.001**
Past medical resource utilization (D-1 ~ D-365)				
Prescription for urate-lowering therapy (%)	212 (15.0)	96 (10.0)	89 (19.3)	**<0.001**
Prescription for acute gout treatment (%)	312 (22.0)	224 (23.4)	88 (19.1)	0.075
Outpatient visits for gout (%)	116 (8.2)	74 (7.7)	42 (9.1)	0.437
Previous hospitalisation for primary diagnosis of gout (yes/no) (%)	79 (5.6)	22 (2.3)	62 (13.4)	**<0.001**
Previous ED attendance (yes/no) (%)	628 (44.3)	361 (37.8)	264 (57.3)	**<0.001**
Radiographs in the ED				
Had at least one radiograph (%)	706 (49.8)	463 (48.4)	243 (52.7)	0.146
On any lower limb joints^ (%)	610 (43.0)	403 (42.2)	207 (44.9)	0.357
On any upper limb joints^ (%)	129 (9.1)	74 (7.7)	55 (11.9)	**0.014**
Number of joints involved (median [Q1, Q3])	0.0 [0.0,1.0]	0.0 [0.0,1.0]	1.0 [0.0,1.0]	**0.001**

^lower limb includes ankle, knee and foot; upper limb includes hand, wrist, elbow and shoulder

Table 2: Adjusted odds ratios, 95% confidence intervals and coefficients for the odds of hospitalization

Variable	OR	95% CI	p-Value	Final Coef.
Intercept	0.03	[0.01, 0.06]	**<0.001**	-3.95
Age	1.04	[1.03, 1.05]	**<0.001**	0.04
Race - Chinese (ref)				
Race - Indian	1.39	[0.94, 2.06]		
Race - Malay	1.07	[0.57, 1.99]		
Race - Others	0.66	[0.38, 1.14]		
Gender - Male	0.79	[0.54, 1.17]		
Hypertension	3.00	[1.97, 4.56]	**<0.001**	1.21
Hyperlipidemia	1.22	[0.76, 1.96]		
Cardiovascular Disease	1.30	[0.82, 2.06]		
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Diabetes	1.12	[0.72, 1.75]		
Chronic Kidney Disease	1.87	[1.23, 2.84]	**<0.01**	0.76
Other comorbidities	0.96	[0.57, 1.63]		
Received urate-lowering therapy	1.04	[0.57, 1.88]		
Received acute gout treatment	0.50	[0.31, 0.80]	**<0.01**	-0.80
Had outpatient visits with gout diagnosis	0.65	[0.31, 1.37]		

Previous hospitalisation for gout	4.88	[2.37, 10.08]	**<0.001**	1.45
Previous ED visits for gout	0.87	[0.59, 1.27]		
Had at least one radiograph	0.60	[0.18, 2.00]		
On any lower limb joints^	0.72	[0.22, 2.30]		
On any upper limb joints^	0.88	[0.24, 3.20]		
Number of joints involved	1.69	[1.20, 2.38]	**<0.01**	

^lower limb includes ankle, knee and foot; upper limb includes hand, wrist, elbow and shoulder

Supplementary Table 1: List of comorbidities included in our analysis. Comorbidity in the Charlson Comorbidity Index were selectively grouped. HIV was not included due to a prevalence of zero in our cohort.

Comorbidities Group	Charlson Comorbidities
Hypertension	N.A.
Hyperlipidemia	N.A.
Cardiovascular Disease	Acute myocardial infarction
	Congestive heart failure
	Cerebral vascular accident
	Peripheral vascular disease
Cancer	Cancer
	Metastatic cancer
Diabetes	Diabetes
	Diabetes complications
Chronic Kidney Disease	Renal Disease
Others	Connective tissue disorder
	Dementia
	Liver disease
	Peptic ulcer
	Pulmonary disease
	Severe liver disease
	Paraplegia

We also tried to add a variable of the number of Charlson comorbidities into the model during our experiments, but we did not present it for the following 3 reasons: 1) it was highly correlated with our existing comorbidity variables, 2) it did not increase the performance of the model, and 3) it is not as easy to collect as our current variables, as the physician may not have access to all the comorbidities of the patient, especially in the primary care setting. We have added a few lines in the discussion section as follows.

Discussion – Paragraph 3

…

We attempted to add a variable of the number of Charlson comorbidities into the model during our experiments, but we did not present it for the following 3 reasons: 1) it was highly correlated with our existing comorbidity variables, 2) it did not increase the performance of the model, and 3) it is not as easy to collect as our current variables, as the physician may not have access to all the comorbidities of the patient, especially in the primary care setting.

RC: ***In the first lines of page 6 you stated "We used easily available clinical and demographic variables, allowing the resultant tool to be usable in an outpatient or primary care setting.". However, a few lines below you wrote that "Additionally, our risk estimation tool is derived from a single centre and from patients who presented to the ED for gout flares, and so may not be generalizable to the outpatient or primary care setting, especially in other populations." I suggest to rephrase them to improve their clarity.***

AR: We thank the reviewer for the advice. We have rephrased it as follows.

Discussion – Paragraph 5

Our study has certain limitations due to its retrospective nature. There may be misclassification of the diagnosis of a gout flare, especially in the patients who were discharged from ED, as it was mainly based on clinical diagnosis by the ED physicians. Additionally, our risk estimation tool is derived from a single centre and from patients who presented to the ED for gout flares, so further validation studies will be required before applying the tool to outpatient or primary care settings, especially in other populations. However, our observations of older age and prior hospitalisation as predictors of hospitalisation are consistent with another local retrospective study [16] investigating the impact of comorbidities, acute illness burden and social determinants of health on the risk of hospital readmissions, and the characteristics and outcomes of our cohort are additionally similar to those described in other developed countries [2,7].
…

RC: ***Due to the retrospective design the study has several limitations, which have been acknowledged by the authors. As a clinician involved in the management of gout flares, I believe that the inclusion of other predictors (such as severity of the gout flare and number or site of joints involved) is extremely important.***

AR: We thank the reviewer for raising this issue. Due to the limitation of our dataset (retrospective administrative data without access to free text notes), these data were unfortunately not available to us. Nevertheless, we made the following attempt. To retrieve severity of the gout flare and number or site of joints involved information without the clinical notes, we proposed a weak hypothesis that when a gout patient visited ED, X-ray orders would be ordered for all the joints affected. Based on this hypothesis, we tried to extract the ED X-ray orders on foot, knee, ankle, hand, shoulder, elbow and wrist from the billing data, and used them to create surrogate markers for 1) the severity of gout flare (whether the patient received an ED X-ray order), 2) the total number of joints involved (number of joints that X-ray was ordered for) and 3) the site of joints involved (whether the X-ray was ordered for joints in upper limb or lower limb). After we conducted the analysis, 1) and 3) were not found to be significant, and 2) were found to be significant but did not increase the performance of the model. We acknowledge the weakness of our attempt as the decision to order an X-ray will depend on individual physician and whether there were already recent X-rays, and further studies will be required to investigate these factors. We have added a few lines in multiple sections as follows.

Materials and Methods – Paragraph 2

…
Ground truth on severity of the gout flare and number or site of joints involved were unavailable in our dataset, however we made the following attempt. We proposed a weak hypothesis that when a gout patient visited ED, radiographs would be ordered for all the joints affected if they were severe. Based on this hypothesis, we extracted the ED foot, knee, ankle and wrist radiograph orders from the billing data, and used them to create surrogate markers for 1) the severity of gout flare (whether the patient received an ED joint radiograph), 2) the total number of joints involved (number of joints that a radiograph was ordered for) and 3) the site of joints involved (whether the radiograph was ordered for upper or lower limb joints).
…

Results – Paragraph 1 & 2

…

Hospitalised patients were more likely to have a radiograph ordered for the upper limb joints (11.9% vs 7.7%) and for more joints (median [IQR] 1.0 [0.0, 1.0] vs. 0.0 [0.0, 1.0]). No significant difference was observed for either whether any radiograph was ordered or whether a radiograph ordered for the lower limb.

…

Table 2 shows the output from the multivariable logistic regression model. Older age and presence of hypertension and chronic kidney disease were associated with higher odds of hospitalisation. Previous hospitalisation for gout was also strongly associated with higher odds of hospitalisation (OR 4.88, 95% CI 2.37-10.08, $p < 0.001$). Prescription of AGT was associated with a lower odds of hospitalization (OR 0.50, 95% CI 0.31-0.80, $p < 0.01$). The number of joints involved was associated with a higher odds of hospitalization (OR 1.69, 95% CI 1.20-2.38, $p < 0.01$). In the final model, we intended to include all variables that had statistically significant adjusted odds ratios. However, we later found that excluding the number of joints involved did not decrease the performance of the model, hence we excluded it for simplicity. The coefficients for these variables as shown in Table 2 were used to build the risk estimator.

Discussion – Paragraph 5

…

Data on severity of the gout flare and number or site of joints involved were similarly unavailable, however we attempted by creating surrogate markers using the radiograph orders. After we conducted the analysis, none of them were included in the final model. We acknowledge the weakness of our attempt as the decision to order a joint radiograph will depend on the individual physician and whether there were already recent radiographs, and further studies will be required to investigate these factors.

…

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Characteristics	Overall	Discharged	Hospitalised	p-Value
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Previous ED attendance (yes/no) (%)	628 (44.3)	361 (37.8)	264 (57.3)	**<0.001**
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Number of joints involved (median [Q1, Q3])	0.0 [0.0,1.0]	0.0 [0.0,1.0]	1.0 [0.0,1.0]	**0.001**

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Chronic Kidney Disease	1.87	[1.23, 2.84]	**<0.01**	0.76
Other comorbidities	0.96	[0.57, 1.63]		
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Had outpatient visits with gout diagnosis	0.65	[0.31, 1.37]		
Previous hospitalisation for gout	4.88	[2.37, 10.08]	**<0.001**	1.45
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Number of joints involved	1.69	[1.20, 2.38]	**<0.01**	

^lower limb joints include ankle, knee and foot; upper limb joints include hand, wrist, elbow and shoulder

2. Reviewer #2

RC: ***In your methods, you excluded inpatients diagnosed with gout but had a primary inpatient diagnosis other than gout. How many patients does it represent above the 5053? This is a limit to apply your model in routine care: how to know in a patient consulting the ED with a gout flare if it is the main diagnosis or not? The "second signal of gout" triggered by another signal such as infection or an acute vascular disease is frequent in this population.***

AR: We thank the reviewer for raising this issue. We are sorry that we did not make ourself understood. We actually did not exclude "inpatients diagnosed with gout but had a primary inpatient diagnosis other than gout", for exactly the reason you mentioned that we may not know whether the patient would be primarily diagnosed with gout in the ED or not. That is why we used the inpatient diagnosis as a confirmation. We have now explicitly mentioned it in the manuscript as follows.

Materials and Methods – Paragraph 1

We conducted a retrospective single-centre cohort study at a tertiary hospital in Singapore, of patients presenting to the ED with a gout flare between 1st January 2015 and 30th September 2017. The patients were identified from the hospital's electronic health record (EHR) system which links the ED attendances, patient's history, previous admissions, laboratory tests, medications and procedures using a unique identifier. The included patients were either diagnosed with gout flare during their ED visit, or hospitalised within 3 days of their latest ED visit with a primary inpatient diagnosis of gout regardless of their primary ED diagnosis. Patients who were diagnosed with gout in ED and hospitalised within 3 days but had a primary inpatient diagnosis other than gout were excluded.

RC: ***Your model does not include non-clinical factors such as social condition and social isolation, functional limitation and pain control, acceptability or not of the hospitalization by the patient. The output probability is not a clear guideline, not relevant and hospitalization is an individual decision.***

AR: We thank the reviewer for raising this issue. We acknowledge that hospitalization, although influenced by ED clinician, is an individualized decision. Non-clinical factors such as socioeconomic status, social condition and social isolation, functional limitation and pain control, post-ED discharge support and acceptability of the hospitalisation would all contribute to the decision, which we were not able to address using our data. Nevertheless, our model's performance was excellent as tested robustly using three different methods, which indicated that clinical factors still play the major role in hospitalisation, and our model could serve as a good clinical reference for individuals before their individualized decision was finally made. We have added a few lines in the discussion section to acknowledge the limitation as follows.

Discussion – Paragraph 5

…
We also acknowledge that the decision for hospitalization, made by the ED clinician, is an individualized decision. Non-clinical factors such as socioeconomic status, social condition and social isolation, functional limitation and pain control, post-ED discharge support and acceptability of the hospitalisation would all contribute to the decision, which we were not able to address using our data. Nevertheless, our model's performance was excellent as tested robustly using three different methods, which indicated that clinical factors still play the major role in hospitalisation, and our model could serve as a good clinical reference for individuals before their individualized decision was finally made.

RC: ***You didn't include colchicine, glucocorticoids and anakinra, which are treatments of flares. Were the patients hospitalized those who did not have these flare prophylactics? Or those who had not had gout treatment in the emergency room? This may be an interesting piece of data in the risk factors for hospitalization.***

AR: We thank the reviewer for the advice. For treatments of flares, in our hospital we used Colchicine, Naproxen, Diclofenac, Ibuprofen, Etoricoxib and Celecoxib. We created a new variable using the outpatient and ED discharge medications with this list. It was found to be borderline insignificant in the univariable analysis while significant in the multivariable analysis, and we have now included it in our final model. Through further analysis, we also found that inclusion of prescription of acute gout therapy increased the regression coefficients of previous hospitalisation for gout or the comorbidities. We suspect that prescription of acute gout therapy could be a suppressor variable, and will explore further in our subsequent studies. We have added a few lines in the results and discussion section as follows.

Materials and Methods – Paragraph 2

…
We defined patients with at least one prescription code for either colchicine, Non-Steroidal Anti-Inflammatory Drugs (NSAID) or COX-2 inhibitors (COXIB) from previous outpatient or ED visits to have stand by acute gout treatment (AGT).
…

Results – Paragraph 1 & 2

…
No significant difference was observed in the prevalence of previous outpatient visits for the management of gout and the prescription code for AGT.
…
Prescription of AGT was associated with a lower odds of hospitalization (OR 0.48, 95% CI 0.30-0.77, $p < 0.01$).
…

Discussion – Paragraph 3

The prescription of AGT was borderline insignificant in the univariable analysis while significant in the multivariable analysis. Through further analysis, we found that the inclusion of AGT prescription increased the regression coefficients of previous hospitalisation for gout or the comorbidities. We suspect that prescription of AGT could be a suppressor variable [15], and will explore further in our subsequent studies.
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(Continue on the next page)

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RC: ***How do you explain the higher frequency of ULT in the hospitalized group? Could this be a collection bias?***

AR: We thank the reviewer for raising this issue. We suspect that higher ULT in the hospitalised group is likely due to this group consisting of older patients with comorbidity who are on follow up in our clinic for chronic disease, as compared to younger patients with only gout without comorbidities who merely visit the emergency department for flare prescriptions and are not on regular follow up. In multivariable analysis, ULT was not a significant predictor of hospitalisation, confirming that the higher rate was due to the confounding effect. We have added a few lines in the discussion section as follows.

Discussion – Paragraph 3

…
Our univariable analysis demonstrated that the hospitalised group had a higher proportion of patients who received ULT in the past 1 year. We suspect the association is likely confounded, as older gout patients with comorbidities tend to be followed up more often in our clinic for chronic diseases, as compared to younger and comparatively healthier gout patients who merely visit the ED for flare prescriptions and are less likely to be regularly reviewed. Our multivariable analysis also revealed that ULT was not a significant predictor of hospitalisation, confirming the confounding effect.
…

RC: ***To my knowledge, older age, a previous hospitalization or ED visit for a given problem are risks factor of hospitalization in themselves. Do you have similar data on other diseases?***

AR: We thank the reviewer for raising this issue. We have searched the literature and found that our observations of older age and previous hospitalisation as predictors for hospitalisation were consistent with another local retrospective study investigating the impact of comorbidities, acute illness burden and social determinants of health on the risk of hospital readmissions. We have added a few lines in the discussion section as follows.

Discussion – Paragraph 5

Our study has certain limitations due to its retrospective nature. There may be misclassification of the diagnosis of a gout flare, especially in the patients who were discharged from ED, as it was mainly based on clinical diagnosis by the ED physicians. Additionally, our risk estimation tool is derived from a single centre and from patients who presented to the ED for gout flares, so further validation studies will be required before applying the tool to outpatient or primary care settings, especially in other populations. However, our observations of older age and prior hospitalisation as predictors of hospitalisation are consistent with another local retrospective study [16] investigating the impact of comorbidities, acute illness burden and social determinants of health on the risk of hospital readmissions, and the characteristics and outcomes of our cohort are additionally similar to those described in other developed countries [2,7].
…

3. Reviewer #3

RC: ***thanks for sharing with us this good work. the strengths of this study is the large number of patients, and also having this study produced in Asia. it doesn't add however to our pre-existing and established understanding of the metabolic Risks associated with Acute Gout, nevertheless it reiterates the fact that hospital admissions with acute Gout, or even intra-hospital gouty attacks, carry significant risks for future morbidity and even mortality. producing and disseminating this message is of interest to our audience.***

AR: We thank the reviewer for the kind comments.