Authors' Response to Round 2 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: *The Authors have answered all my questions. I have no further comments.*

AR: We thank the reviewer for the constructive comments in the first round, which helped us greatly improve the manuscript.

2. Reviewer #2

RC: *In the limit of the retrospective design with unavailable detailed clinical presentation of gout fare, as you acknowledge, joint x-ray is an interesting indirect variable. In your results, is the mean value of number of involved joints also significant? Using mean rather than median is probably better since the majority of your population have 0 or 1 radio.*

AR: We thank the reviewer for the suggestion. We have now changed to use mean value of the number of involved joints when we report the summary statistics in Table 1 and in the Results section as follows. However, it will not change the result of the multivariable logistic regression model as we use the exact number of involved joints during the index ED visit.

Results – Paragraph 1

…
Hospitalised patients were more likely to have a radiograph ordered for the upper limb joints (11.9% vs 7.7%) and for more joints (mean (SD) 0.8 (1.0) vs. 0.6 (0.8)).
…

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 (%)	362 (25.6)	243 (25.4)	120 (26.0)	0.855
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 the lower limb^ (%)	610 (43.0)	403 (42.2)	207 (44.9)	0.357
On the upper limb^ (%)	129 (9.1)	74 (7.7)	55 (11.9)	**0.014**
Number of joints involved (mean (SD))	0.7 (0.8)	0.6 (0.8)	0.8 (1.0)	**<0.001**

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

RC: *The manuscript is well described and bring information about public health issues of gout. However, the model, even if robust and tested, is difficult to apply in clinical practice.*

AR: We thank the reviewer for the comment. We plan to apply our model in outpatient or primary care settings to prioritise people at risk for hospitalisation for higher level of resource allocation. Gout should mainly be managed in primary care, but complex gout may be better managed otherwise. The intent is not to use it in ED to decide admission, as that would be a circular reasoning. We have added a few words in the discussion section as follows.

Discussion – Paragraph 1

We have described a large dataset of patients with gout, and the factors associated with hospitalisation after an ED visit, and created an easy to use, web-based risk estimation tool, to estimate the risk of hospitalisation for patients with gout. We plan to apply our tool in outpatient or primary care settings to prioritise people at risk for hospitalisation for a higher level of resource allocation such as early specialist review, managed care and / or more frequent review.

RC: *It is however reassuring that treating flares decreased hospitalizations for gout, but it rises another question: why patients hospitalized from ED have been less treated? Contra-indication for flare medications, unrecognition of gout by the ED?*

AR: We thank the reviewer for raising the question. If we understand correctly, you are referring to the lower prevalence of patients who have received acute flare medications in Table 1. After our inclusion of prednisolone in the acute flare medications, we no longer see that patients hospitalized are less treated in the univariable analysis. In the multivariable analysis, we agree with you that treating flares decrease hospitalizations for gout, so patients suffering from untreated flare are more likely to be hospitalized. We have added a few sentences in the discussion section as follows.

Discussion – Paragraph 3

The prescription of AGT was 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. The analysis suggests that patients suffering from untreated gout flares were more likely to be hospitalized and treating flares with appropriate medications decreased hospitalization for gout.

…

RC: *Is prednisone have been taken account in acute flares medication?*

AR: We thank the reviewer for raising the question. We sincerely apologise for the omission, and have now included prednisolone in the acute flares medication list and updated the manuscript as follows. Most of the coefficients are changed as a result, but the final model and conclusions we draw from the analysis remain the same.

Materials and Methods – Paragraph 2

…
We defined patients with at least one prescription code for either prednisolone, 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).
…

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

Variable	OR	95% CI	p-Value	Final Coef.
Intercept	0.02	[0.01, 0.06]	**<0.001**	-3.99
Age	1.04	[1.03, 1.05]	**<0.001**	0.04
Race - Chinese (ref)				
Race - Indian	1.39	[0.94, 2.06]		
Race - Malay	1.06	[0.57, 1.97]		
Race - Others	0.67	[0.39, 1.15]		
Gender - Male	0.78	[0.53, 1.16]		
Hypertension	3.04	[2.00, 4.62]	**<0.001**	1.22
Hyperlipidemia	1.20	[0.75, 1.92]		
Cardiovascular Disease	1.32	[0.84, 2.08]		
Cancer	1.94	[0.88, 4.32]		
Diabetes	1.12	[0.72, 1.74]		
Chronic Kidney Disease	1.89	[1.25, 2.88]	**<0.01**	0.77
Other comorbidities	0.97	[0.58, 1.64]		
Received urate-lowering therapy	1.02	[0.56, 1.86]		
Received acute gout treatment	0.61	[0.39, 0.96]	**<0.05**	-0.62
Had outpatient visits with gout diagnosis	0.62	[0.29, 1.30]		
Previous hospitalisation for gout	4.80	[2.34, 9.85]	**<0.001**	1.39
Previous ED visits for gout	0.83	[0.57, 1.22]		
Had at least one radiograph	0.59	[0.18, 1.96]		
On any lower limb joints^	0.73	[0.23, 2.33]		
On any upper limb joints^	0.90	[0.25, 3.22]		
Number of joints involved	1.70	[1.20, 2.39]	**<0.01**	

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

RC: *In brief, suffering of an untreated gout (no flare medications) and have been recently hospitalized for gout when suffering of risks factors of gout (hypertension and CKD) is associated to a high risk of hospitalization. Suffering of an untreated disease is probably by the way a strong determinant of hospitalization for these disease.*

AR: We thank the reviewer for the comment. We agree with you that suffering of an untreated disease is probably a strong determinant of hospitalization for such diseases.

RC: *A final question is: where do you place, for the clinician, your model in the management of patients with gout who goes to ED? Concretely, for example a patient with a LR of hospitalization of 34%: what should be done, hospitalization or not?*

AR: We thank the reviewer for raising the issue. As we mentioned above, we plan to apply our model in outpatient or primary care settings to prioritise people at risk for hospitalisation for higher level of resource allocation. The model derives risk of hospitalisation from ED attendances, however it is not intended to be used in ED, as that would be a circular reasoning. We hope it can recognises patients who are at higher risk of hospitalisation in the outpatient or primary care settings with simple variables, so that more resources can be diverted to them, in the form of early specialist review, managed care, more frequent review etc. Concretely, we calculated the median of predicted risk scores for both

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Discussion – Paragraph 1

We have described a large dataset of patients with gout, and the factors associated with hospitalisation after an ED visit, and created an easy to use, web-based risk estimation tool, to estimate the risk of hospitalisation for patients with gout. We plan to apply our tool in outpatient or primary care settings to prioritise people at risk for hospitalisation for a higher level of resource allocation such as early specialist review, managed care and / or more frequent review.

Discussion – Paragraph 2

…

The median of predicted risk scores is 0.60 for hospitalised patients versus 0.14 for discharged patients. Depending on the further external validation, we may choose, for example, a cut off score of 0.6 for a dichotomized recommendation of specialist care versus primary care.

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3. Reviewer #3

RC: Accept in current format.

AR: We thank the reviewer for your kind opinion.