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# Hemoglobin-to-RDW ratio, hemoglobin-to-monocyte ratio, and hemoglobin-to-leukocyte ratio are predictive of 14-day readmission after primary total knee arthroplasty

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## Abstract

**Background** Total knee arthroplasty (TKA) is an effective treatment for knee osteoarthritis; however, early readmissions due to complications are common. This study assessed the ability of the hemoglobin-to-red cell distribution width ratio (HRR), hemoglobin-to-monocyte ratio (HMR), and hemoglobin-to-leukocyte ratio (HLR) to predict readmission within 14 days after TKA.

**Methods** Data from the Chang Gung Medical Research Database (CGRD) from 2014 to 2022 were retrospectively analyzed. Patients  $\geq 20$  years old who underwent primary TKA were eligible for inclusion. Patients with incomplete data on the indices of interest or follow-up  $< 14$  days were excluded. Patient demographic, clinical, and comorbidity data were collected. Logistic regression was utilized to determine the associations between HRR, HMR, and HLR and 14-day readmission.

**Results** Data from 1,137 patients were analyzed. Multivariable analysis revealed that a higher HMR was significantly associated with lower 14-day readmission risk (adjusted OR [aOR] = 0.72, 95% confidence interval [CI]: 0.51–0.997), an HMR  $\geq 2.18$  (optimal cutoff value) was predictive of a significantly lower 14-day readmission risk (aOR = 0.61, 95% CI: 0.39–0.96). The composite indicator, HRR-HMR-HLR score, derived from the 3 indices assessed, was significantly associated with a lower 14-day readmission risk (score 2 vs. score 0: aOR = 0.51, 95% CI: 0.27–0.98; score 3 vs. score 0: aOR = 0.37, 95% CI: 0.17–0.82).

**Conclusions** High HMR and the HRR-HMR-HLR score are independently associated with a lower 14-day readmission risk after TKA. Implementing these indices into clinical practice may enhance postoperative management.

**Keywords** Risk factors, Predictive biomarkers, Complete blood count (CBC) ratios, Chang Gung medical research database (CGRD), Knee surgery

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## Background

Total knee arthroplasty (TKA) is commonly performed for treating severe knee arthritis and can relieve pain and restore function [1, 2]. The primary indications for TKA include osteoarthritis, rheumatoid arthritis, and post-traumatic arthritis, all of which can lead to significant joint pain, swelling, and stiffness [3, 4]. Over the past 2 decades, the frequency of performing TKA has steadily increased, particularly in industrialized countries where the annual frequency ranges from 150 to 200 procedures per 100,000 persons [5]. Despite advancements in surgical techniques and postoperative care, a notable proportion of patients experience early complications and require readmission shortly after surgery [6, 7].

In recent years, indices based on different blood components have emerged as potential markers for predicting outcomes in various medical conditions [8, 9]. The hemoglobin-to-red cell distribution width ratio (HRR) is calculated by dividing the hemoglobin level by the red cell distribution width, and it reflects the balance between oxygen-carrying capacity and erythrocyte variability [10]. The hemoglobin-to-monocyte ratio (HMR) is the ratio of hemoglobin to the number of monocytes and reflects the interplay between oxygen transport and the immune response. The hemoglobin-to-leukocyte ratio (HLR) is the ratio of hemoglobin to the total leukocyte count and represents the relation between oxygen delivery and overall inflammatory status. These ratios have been less studied compared to others such as the leukocyte-to-albumin ratio, and as such more study is warranted to examine their potential clinical applications. A previous study reported that low hemoglobin levels were associated with adverse outcomes, including higher readmission rates after total joint arthroplasty [11], while elevated preoperative RDW levels were also linked to increased readmission following the procedure [12]. This prompted us to consider that the combination of hemoglobin and RDW—namely, the HRR—may enhance risk stratification for readmission following TKA, along with other related composite markers such as HMR and HLR.

Thus, the purpose of this study was to his study aims to investigate the predictive value of the HRR, HMR, and HLR for 14-day readmission after primary TKA. By identifying reliable markers for early readmission, healthcare providers can better stratify patients based on their risk and implement targeted interventions to improve postoperative outcomes [13, 14]. Understanding the role of these hematological ratios in the context of TKA could provide valuable insights into the management and follow-up care of patients undergoing this common orthopedic procedure.

## Methods

### Data source

Data of patients who received a primary TKA between 2014 and 2022 were collected from the Chang Gung Medical Research Database (CGRD). The CGRD is a comprehensive and invaluable resource for clinical and epidemiological research in Taiwan. Established by Taiwan's Chang Gung Medical Foundation, the CGRD is compiled from the extensive network of Chang Gung Memorial Hospitals, the largest healthcare network in Taiwan. This network includes multiple hospitals and medical centers that provide a wide range of healthcare services, making the CGRD one of the most extensive and detailed medical databases in the country.

### Study design and population

This population-based retrospective study included patients  $\geq 20$  years old who underwent primary TKA performed by a single surgeon (W.C.C.) between 2014 and 2022. Patients with missing information on data of interest and those with follow-up of  $< 14$  days were excluded.

### Variables and main outcome

Data extracted from the medical records included patient age, sex, body mass index (BMI), and comorbidities such as hypertension, ischemic heart disease, diabetes, osteoporosis, chronic kidney disease (CKD), chronic pulmonary disease, and rheumatic diseases. For each patient, the Charlson Comorbidity Index (CCI) was calculated based on the information in the medical records [15]. Additional data extracted included laboratory information, anticoagulant prophylaxis, intraoperative blood loss, the duration of the operation, and if the patient was readmitted within 14 days after the surgery. Laboratory information extracted was used to calculate the HRR, HMR, and HLR, and they were examined as potential indicators of readmission following primary TKA. The blood biomarkers were collected within a time window ranging from one month prior to surgery to one-week post-surgery, with the value closest to the day of surgery being used for analysis. The primary outcome was hospital readmission for any cause within 14 days after TKA.

In addition, we developed a clinical scoring system based on the HRR, HMR, and HLR called the "HRR-HMR-HLR score", and examined the predictive ability of the score for readmission within 14 days after surgery. A score of 0 indicates no high level (above their optimal cutoff thresholds) for all three indices, a score of 1 indicates a high level for one of the three, a score of 2 indicates a high level for two of the three, and a score of 3 indicates a high level for all three measures.

### Ethics statement

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The requirement of informed patient consent was waived because of the retrospective nature of the study and the use of de-identified patient data such that no individual could be identified from the data used in this study.

### Statistical analysis

Continuous data were presented as mean  $\pm$  standard deviation, median (minimum-maximum), and categorical data were presented as number (%). Logistic regression analyses were used to calculate p-values for group comparisons. Univariate and multivariable regression analyses were performed to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for 14-day readmission rates. Multivariate analyses were adjusted for variables with a p-value  $< 0.15$  in the univariate analysis (except for laboratory data), including age, sex, prophylactic anti-coagulant used, operative duration, and intraoperative blood loss. All p values were 2-sided, and  $p < 0.05$  was considered to indicate a statistically significant difference. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

## Results

### Patient inclusion

A total of 1,270 patients  $\geq 20$  years old who underwent a primary TKA were identified in the database. Patients with missing laboratory data ( $n=67$ ) and those with a follow-up of  $< 14$  days ( $n=66$ ) were excluded. Thus, 1,137 patients were included in the analysis.

### Patient characteristics

Patient characteristics, all patients, and those that were and were not readmitted within 14 days are summarized in Table 1 and Supplementary Table 1. The mean age of all patients was 70 years, 75% were female (Table 1), and the most common comorbidity was hypertension (72%) (Supplementary Table 1).

The optimal thresholds of HRR, HMR, and HLR for predicting 4-day readmissions after TKA were established using receiver operating characteristic (ROC) curve analysis (Supplementary Tables 2 and Supplementary Fig. 1).

In the univariate analysis, an HMR level greater than the optimal threshold was significantly associated with a lower risk of 14-day readmission (35% vs. 47%, crude OR=0.61, 95% CI: 0.39–0.95,  $p=0.027$ ) as compared to a value less than the optimal threshold (Table 1).

**Table 1** Patient characteristics

Study variable	Total (N= 1,137)	14-Day Readmission		OR (95% CI)	p-value
		Yes (n= 95)	No (n= 1,042)		
<b>HRR</b>	1.0 $\pm$ 0.2; 1.0 (0.4–1.4)	1.0 $\pm$ 0.2; 1.0 (0.6–1.3)	1.0 $\pm$ 0.2; 1.0 (0.4–1.4)	0.88 (0.23, 3.38)	0.857
< Optimal threshold (< 0.81)	175 (15.4)	19 (20.0)	156 (15.0)	1.00 (reference)	
$\geq$ Optimal threshold ( $\geq$ 0.81)	962 (84.6)	76 (80.0)	886 (85.0)	0.70 (0.41–1.20)	0.195
<b>HMR</b>	2.3 $\pm$ 2.0; 2.1 (0.7–47.0)	2.1 $\pm$ 0.6; 2.0 (0.8–3.8)	2.4 $\pm$ 2.1; 2.1 (0.7–47.0)	0.73 (0.53–1.00)	<b>0.048</b>
< Optimal threshold (< 2.18)	618 (54.4)	62 (65.3)	556 (53.4)	1.00 (reference)	
$\geq$ Optimal threshold ( $\geq$ 2.18)	519 (45.6)	33 (34.7)	486 (46.6)	0.61 (0.39–0.95)	<b>0.027</b>
<b>HLR</b>	1.9 $\pm$ 0.5; 1.9 (0.7–3.9)	1.9 $\pm$ 0.5; 1.8 (0.8–3.6)	1.9 $\pm$ 0.5; 1.9 (0.7–3.9)	0.89 (0.59–1.34)	0.568
< Optimal threshold (< 1.93)	615 (54.1)	58 (61.1)	557 (53.5)	1.00 (reference)	
$\geq$ Optimal threshold ( $\geq$ 1.93)	522 (45.9)	37 (38.9)	485 (46.5)	0.73 (0.48–1.13)	0.156
<b>Demography</b>					
Age, years	70.2 $\pm$ 8.6; 71.0 (29.0–101.0)	70.4 $\pm$ 8.6; 71.0 (29.0–101.0)	69.0 $\pm$ 8.9; 70.0 (39.0–89.0)	0.98 (0.96–1.01)	0.143
20–49	15 (1.3)	4 (4.2)	11 (1.1)	1.00 (reference)	
50–59	104 (9.1)	10 (10.5)	94 (9.0)	0.29 (0.08–1.09)	0.067
60–69	396 (34.8)	33 (34.7)	363 (34.8)	0.25 (0.08–0.83)	<b>0.023</b>
70–79	472 (41.5)	42 (44.2)	430 (41.3)	0.27 (0.08–0.88)	<b>0.030</b>
80+	150 (13.2)	6 (6.3)	144 (13.8)	0.11 (0.03–0.47)	<b>0.003</b>
Sex					
Male	288 (25.3)	31 (32.6)	257 (24.7)	1.00 (reference)	
Female	849 (74.7)	64 (67.4)	785 (75.3)	0.68 (0.43–1.06)	0.089

AST, aspartate aminotransferase; HRR, hemoglobin-to-RDW ratio; HMR, hemoglobin-to-monocyte ratio; HLR, hemoglobin-to-leukocyte ratio; OR, odds ratio; RBC, red blood cells; RDW, red cell distribution width; CI, confidence; WBC, white blood cells

Continuous variables are presented as mean  $\pm$  standard deviation; median (minimum-maximum)

Categorical variables are presented as counts (percentage)

p-value  $< 0.05$  are shown in bold

**Table 2** Associations between HRR, HMR, HLR, and 14-day readmission after primary TKA ( $n = 1,135$ )

	14-Day Readmission	
	aOR <sup>a</sup> (95% CI)	p-value
<b>HRR</b>	0.72 (0.19–2.78)	0.632
< Optimal cutoff	1.00 (reference)	
≥ Optimal cutoff	0.70 (0.41–1.21)	0.203
<b>HMR</b>	<b>0.72 (0.51–0.997)</b>	<b>0.048</b>
< Optimal cutoff	1.00 (reference)	
≥ Optimal cutoff	<b>0.61 (0.39–0.96)</b>	<b>0.034</b>
<b>HLR</b>	0.85 (0.56–1.29)	0.442
< Optimal cutoff	1.00 (reference)	
≥ Optimal cutoff	0.69 (0.44–1.08)	0.101

HRR, hemoglobin-to- RDW ratio; HMR, hemoglobin-to-monocyte ratio; HLR, hemoglobin-to-leukocyte ratio; aOR, adjusted odds ratio; CI, confidence interval

P-values < 0.05 are shown in bold

<sup>a</sup> Adjusted for related variables of p-value < 0.15 in univariate analysis (except for lab variables), including age, sex, DOACs, intraoperative blood loss, and operative duration

**Table 3** Associations between HRR-HMR-HLR score and 14-day readmission after primary TKA ( $n = 1,135$ )

	14-Day Readmission	
	aOR <sup>a</sup> (95% CI)	p-value
HRR-HMR-HLR score		
Score 0	1.00 (reference)	
Score 1	0.68 (0.34–1.35)	0.267
Score 2	<b>0.51 (0.27–0.98)</b>	<b>0.043</b>
Score 3	<b>0.37 (0.17–0.82)</b>	<b>0.015</b>

HRR, hemoglobin-to-RDW ratio; HMR, hemoglobin-to-monocyte ratio; HLR, hemoglobin-to-leukocyte ratio; aOR, adjusted odds ratio; CI, confidence interval

P-values < 0.05 are shown in bold

<sup>a</sup> Adjusted for related variables of p-value < 0.15 in univariate analysis (except for lab variables), including age, sex, DOACs, intraoperative blood loss, and operative duration

### Multivariable analysis of the associations between HRR, HMR, and HLR and 14-day readmission

Associations between HRR, HMR, and HLR and 14-day readmission are summarized in Table 2. After adjusting for relevant confounders in the multivariable analysis, the results showed that the higher the HMR value, the lower the risk of 14-day readmission (adjusted OR [aOR]=0.72, 95% CI: 0.51–0.997,  $p=0.048$ ). An HMR value greater than the optimal cutoff was associated with a significantly lower risk of 14-day readmission (aOR=0.61, 95% CI: 0.39–0.96,  $p=0.034$ ) compared to a value below the optimal cutoff (Table 2).

### HRR-HMR-HLR score in predicting 14-day readmission

Associations between the HRR-HMR-HLR score and 14-day readmission are summarized in Table 3. After adjusting for relevant confounders in the multivariable analysis, we found that patients with an HRR-HMR-HLR score 2 (aOR=0.51, 95% CI: 0.27–0.98,  $p=0.043$ ) and score 3 (aOR=0.37, 95% CI: 0.17–0.82,  $p=0.015$ ) had

significantly lower risks of 14-day readmission as compared with score 0 (Table 3).

### Discussion

This study evaluated the predictive value of 3 novel routine blood test-derived markers, HRR, HMR, and HLR, for 14-day readmission risk after a TKA. Our results showed that a high HMR ( $\geq 2.18$ ), incorporating hemoglobin and monocyte counts, was the strongest predictor of reduced 14-day readmission risk, suggesting that this simple biomarker may be useful for predicting post-operative outcomes. A high HRR and HLR, while not as strongly predictive as HMR, still showed trends toward association with 14-day readmission rates. Furthermore, the composite score combining these 3 markers, the HRR-HMR-HLR score, was found to predict a lower risk of 14-day readmission. In summary, these findings indicate that these hematologic biomarkers, particularly HMR, along with the HRR-HMR-HLR score composite score, may serve as valuable indicators for early readmission risk. However, further investigations to explore the underlying physiological mechanisms, and to examine their prognostic value in prospective studies are still needed.

Various studies in the literature have examined the usefulness of hematologic markers, especially those derived from routine blood tests, concerning perioperative outcomes of arthroplasty including deep vein thrombosis (DVT), loosening, and readmission. In a rather unique study, Xiong et al. [16] studied predictors of preoperative DVT in patients undergoing TKA or THA and reported that decreased RBC count, lower hemoglobin level, elevated RDW-coefficient of variation, and higher RDW-standard deviation were significant predictors of preoperative DVT. Bozgeyik et al. [17] reported that, in patients who underwent TKA, the monocyte-to-lymphocyte ratio (MLR) was significantly different between patients with and without aseptic loosening, a serious complication after TKA. The findings are notable because no other parameters have been defined to be associated with aseptic loosening. On the other hand, using data from the American College of Surgeons National Quality Improvement Programme registry, Khoshbin et al. [18] examined preoperative albumin level, hematocrit, platelet count, and WBC count for their value in predicting readmission after THA and TKA. The results showed that in patients undergoing THA or TKA, a preoperative albumin level of < 35 g/l was associated with a 1.5- to 1.8-times increased odds of readmission within 30 days. Although not the same as our primary biomarkers, these researches underscore a sustained interest in identifying simple and accessible blood biomarkers for short-term outcomes of joint replacement. This also highlights that

few studies have explored the specific markers examined in this research.

Our results showed that a high HMR value, incorporating hemoglobin and monocyte counts, was associated with a decreased risk of readmission within 14 days of TKA, suggesting that this simple marker may be useful for predicting postoperative outcomes. No prior report has yet directly evaluated the prognostic value of HMR in orthopedic surgical settings. Nevertheless, one study by Jones et al. [19] evaluated whether biomarkers derived from complete blood count ratios predict adverse events after THA and TKA, and indicated that the elevation of the monocyte-to-lymphocyte ratio (MLR), a biomarker that incorporates monocyte counts, is associated with a length of stay (LOS) of  $\geq 3$  days following both TKA and THA. In a study examining predictors of acute DVT following TKA, elevated MLR was significantly correlated with the risk of postoperative DVT [20]. However, HMR, which also incorporates monocyte counts, was not mentioned or assessed in the studies cited above.

We further established that a higher HRR-HMR-HLR score is associated with a lower 14-day readmission rate following TKA. This suggests that this score could be a candidate marker in the prognostification of TKA. Specifically, these three ratios are all based on hemoglobin; one includes RDW, while the other two incorporate monocyte and leukocyte counts. We shall emphasize again that, currently, no study has assessed the significance of these three ratios, either individually or combined, in orthopedic settings, necessitating the extrapolation of insights from the components of the ratios. In a relevant study of patients undergoing total joint arthroplasty (TJA), a higher RDW was linked to worse postoperative outcomes [21]. Furthermore, Brumat et al. [22] attempted to identify predictors of prosthetic joint infection (PJI) in patients who received TJA. Their results showed that the product of the leukocyte count performed preoperatively and on postoperative day 2  $> 100$  was 97% specific for a high-grade PJI. In our study, a higher HRR-HMR-HLR score, potentially indicative of lower monocyte and leukocyte counts, was associated with a favorable outcome (reduced risk of readmission). This aligns partially with findings from the abovementioned studies, where an elevated RDW or leukocyte count metric was associated with poor outcomes of TJA.

Regarding potential mechanistic explanations, higher hemoglobin levels—integral to our ratios and composite indices—are associated with enhanced oxygen delivery to tissues, improved immune function, and better physical performance, which are crucial factors in post-surgical recovery [23, 24]. While these mechanisms may offer plausible explanations for our observations (assuming the results are robust), the current study design is not equipped to directly investigate the underlying pathways.

Instead of clarifying these mechanisms, our analysis serves as a preliminary exploration of the potential clinical utility of these markers. Future prospective or experimental studies will be essential to confirm their validity for routine clinical use and the mechanistic explanations.

### Strengths and limitations

A major strength of this study is the use of a large, comprehensive dataset from the CGRD, which provides robust data for analysis. Additionally, focusing on a single surgeon's cases ensures consistency in surgical technique and postoperative care, reducing variability. However, the study has several limitations. The retrospective design may introduce selection bias, and the exclusion of patients with missing data could affect the generalizability of the findings. Furthermore, while we adjusted for various confounders, there may still be unmeasured variables that influence readmission rates. Additionally, the ROC curve analysis employed for determining the cutoff values demonstrated relatively weak performance, as indicated by the AUC values. Among the biomarkers analyzed, only the HRR exhibited high sensitivity. The wide 95% confidence intervals in the ORs suggest considerable variability, which may affect the reliability of the observed associations. Cautions should be taken while interpreting our findings.

### Conclusion

This study demonstrated that, among the biomarkers analyzed, a high HMR ( $\geq 2.18$ ) has the strongest association with 14-day readmission risk in patients undergoing TKA, underscoring its potential utility. Additionally, the composite HRR-HMR-HLR score effectively stratified readmission risk, further emphasizing its clinical utility. However, further studies are needed to validate these findings before they can be integrated into perioperative care protocols.

### Abbreviations

TKA	Total knee arthroplasty
HRR	Hemoglobin-to-red cell distribution width ratio
HMR	Hemoglobin-to-monocyte ratio
HLR	Hemoglobin-to leukocyte ratio
CGRD	Chang Gung Medical Research Database

### Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13018-024-05116-w>.

Supplementary Material 1

### Acknowledgements

This study is based in part on data from the Chang Gung Research Database provided by Chang Gung Memorial Hospital. The interpretation and conclusions contained herein do not represent the position of Chang Gung Memorial Hospital.



The authors thank the statistical assistance and wish to acknowledge the support of the Maintenance Project of the Center of Data Science and Biostatistics (Grant CLRPG2C0021, CLRPG2C0022, CLRPG2C0023, CLRPG2C0024, CLRPG2G0081, CLRPG2G0082, CLRPG2G0083, CLRPG2L0021, and CLRPG2L0022) at Chang Gung Memorial Hospital for study design and monitor, data analysis and interpretation.

#### Author contributions

Ngi-Chiong Lau: guarantor of integrity of the entire study; study concepts; study design; definition of intellectual content; clinical studies; data analysis; statistical analysis; manuscript preparation; manuscript editing; manuscript review Chih-Chien Hu: literature research; experimental studies; data acquisition; data analysis; statistical analysis; manuscript preparation Yu-Yi Huang: clinical studies; data acquisition; data analysis; statistical analysis; study design; manuscript editing; manuscript review Pin-Ren Huang: study design; definition of intellectual content; clinical studies; data analysis Dave W. Chen: clinical studies; data analysis; statistical analysis; manuscript preparation; manuscript review All authors reviewed and approved the final version of the manuscript.

#### Funding

None.

#### Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

#### Declarations

##### Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. The requirement of informed patient consent was waived because of the retrospective nature of the study and the use of de-identified patient data such that no individual could be identified from the data used in this study.

##### Consent for publication

Not applicable.

##### Competing interests

The authors declare no competing interests.

Received: 11 July 2024 / Accepted: 25 September 2024

Published online: 26 October 2024

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