# Factors affecting patient-reported outcomes after red blood cell transfusion in medical patients

*Ka Lok Luke Chan,[1] Wai Man Vivien Mak,[1] Yat Hung Tam,[2] and Kwok Kuen Harold Lee[1]*

**BACKGROUND:** Physical variables like mortality or cardiac events were used to evaluate the requirement of red blood cell (RBC) transfusion. However, patient-reported outcomes (PROs) of blood transfusion recipients were seldom assessed. The health-related quality of life (HRQoL) of patients before and after RBC transfusion was compared in this study.

**STUDY DESIGN AND METHODS:** The study period was February to June 2016. Standardized generic and anemia symptom-specific HRQoL instruments were administered to patients receiving RBC transfusion in the medical unit of a single center. The primary outcome was the change in HRQoL scores on Days 1 and 7 posttransfusion from baseline values on the day of transfusion (Day 0). Multiple linear regression analysis was performed to study the effect of transfusion strategy and other factors on PRO.

**RESULTS:** The analysis included 99 general medical patients. The median (interquartile range) pretransfusion hemoglobin level was 72 (66-78) g/L. Two or more units of RBCs were prescribed to 45 patients (45%) on Day 0. Functional Assessment of Cancer Therapy-Anemia Subscale improved significantly on Days 1 and 7 by effect sizes of 0.41 and 0.38, respectively ($p < 0.001$). Regression analysis showed that lower baseline HRQoL scores were associated with better PRO on both Day 1 and Day 7 ($p < 0.001$). Transfusion trigger and number of RBC units transfused did not affect the change in HRQoL.

**CONCLUSION:** Worse pretransfusion HRQoL is a predictor of improvement in PRO after blood transfusion. There is no evidence that a restrictive transfusion or single-unit policy jeopardizes PRO.

Blood transfusion is one of the most frequently performed medical procedures. Although it is safe in general, patients are exposed to the risk of unnecessary morbidity or rarely mortality if the transfusion is not indicated.[1] The demand for blood products is increasing because of an aging population in affluent society and the advance in treatment like surgical procedures and chemotherapy.[2] Patient blood management is advocated to reduce the need for allogeneic blood products transfusion.[1,3,4] Randomized controlled trials suggested that restrictive red blood cell (RBC) transfusion using a hemoglobin (Hb) concentration of 70 to 80g/L as the transfusion trigger was not inferior to a more liberal strategy in terms of all-cause mortality, cardiac events, length of hospital stay, and functional recovery.[5,6] Restrictive transfusion is therefore recommended in various

**ABBREVIATIONS:** CCI = Charlson's Comorbidity Index; FACT-AnS = Functional Assessment of Cancer Therapy-Anemia Subscale; HRQoL = health-related quality of life; IQR = interquartile range; MCS = mental component summary; MEWS = Modified Early Warning Scores; PCS = physical component summary; PRO(s) = patient-reported outcome(s).

From the [1]Division of Haematology, Department of Medicine and Geriatrics, Princess Margaret Hospital, Kwai Chung, Hong Kong; and the [2]School of Public Health, The University of Hong Kong, Pokfulam, Hong Kong.

*Address reprint requests to*: Chan Ka Lok Luke, Division of Haematology, Department of Medicine and Geriatrics, Princess Margaret Hospital, Kwai Chung, Hong Kong; e-mail: ckl5141@ha.org.hk.

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guidelines on transfusion practice. Transfusion requirement in specific situations like ischemic heart disease and perioperative care was also discussed in these guidelines.[7-9] In general medical patients, the recommendation of restrictive RBC transfusion was derived from studies in critical care and perioperative settings instead of being supported by direct evidence.[7] These patients, however, have different clinical characteristics. General medical patients consist of a large proportion of elderly individuals. They often have a high burden of chronic illnesses and the etiologies of anemia are multifactorial. Age and comorbidity can affect one's tolerance to anemia and susceptibility to transfusion-related complications.[10] The transfusion requirement of general medical patients ought to be studied specifically to enhance the precision in practice.

### Health-related quality of life of patients with anemia

Anemia is associated with impaired overall well-being, physical activity, and functional status.[11] Outcome measures in previous studies on transfusion practice included all-cause mortality, cardiac events, and length of hospital stay. Patient-reported outcomes (PROs) were seldom evaluated. A possible explanation is that transfusion requirements were usually studied in postoperative or intensive care patients. Health-related quality of life (HRQoL) assessment was either impossible or easily confounded by other factors.

HRQoL instruments focusing on health status of patients with anemia and response to intervention were developed.[12,13] For example, erythropoietin (EPO)-stimulating agents improve the HRQoL of patients with chronic kidney disease and myelodysplastic syndrome by improving Hb level.[14-16] The use of these instruments to study the effect of RBC transfusion was only limited to a few conditions like advanced cancer and myelodysplastic syndrome.[17,18]

In this study, we compared the HRQoL of medical patients before and after RBC transfusion. Factors associated with PROs in transfusion recipients were also determined.

## MATERIALS AND METHODS

### Research institution and subjects

This was a single-center study carried out at the medical department of Princess Margaret Hospital in Hong Kong during February to June 2016. There was no specific recommendation on the transfusion trigger in the hospital transfusion guidelines. RBC transfusions were initiated by attending clinicians according to their clinical judgment.

Inpatients and outpatients aged 18 years or older receiving RBC transfusion between 9 AM and 5 PM, Monday to Friday were recruited for the study. Exclusion criteria were unstable hemodynamics or oxygen saturation, altered mental status, cognitive impairment, or not understanding Chinese or English. Regularly transfused patients, for example, patients with thalassemia major, were also excluded. Patients who had participated in the study would not be recruited again. Patients who had ongoing bleeding symptoms during the follow-up period were excluded from data analysis. The study was approved by the local ethics committee. Written consent was obtained from all participants.

### Data collection

Collected data included patients' demographics, history of chronic anemia defined as steady-state Hb level of less than 100 g/L over the past 3 months, transfusion requirement in the past 1 week before recruitment, Charlson's Comorbidity Index (CCI),[19] transfusion trigger denoted by the pretransfusion Hb concentration, and number of RBC units administered on the day of recruitment (Day 0). Medical records were evaluated for the presence of acute anemia, defined as decrease from steady-state Hb by more than 10g/L over the past 7 days. Modified Early Warning Scores (MEWS)[20] were measured on Days 0 and 1 to compare the change in physiologic variables. Hb level was repeated on Days 1 and 7 when clinically indicated. The occurrence of transfusion-related complications, additional RBC units transfused during Day 1 to Day 7, and the length of hospital stay of inpatients were retrieved.

Two HRQoL instruments, the acute form of Chinese (HK) Short Form 12 Version 2 (SF-12v2)[21] and Functional Assessment of Cancer Therapy-Anemia Subscale (FACT-AnS),[12] were administered to subjects on Days 0, 1, and 7, respectively. The first assessment was performed before RBC transfusion. The second assessment was performed on Day 1 because the Hb concentration would have equilibrated in most patients by that time.[22] We made the third assessment on Day 7 because the recall period of both instruments is 7 days. The questionnaires were self-administered. Telephone interviews were conducted in discharged patients with the questionnaires read verbatim by trained staff.

### Study instruments

SF-12v2 is a generic measure of health status in different domains. A physical component summary (PCS) and mental component summary (MCS) score could be derived from the survey.[21] Higher scores indicate better HRQoL. The validity and sensitivity of the survey in Hong Kong Chinese adults were established.[23,24] The acute form of SF-12v2 with a recall period of 7 days was adopted in this study to better reflect acute change in health status after blood transfusion.[25]

Functional Assessment of Cancer Therapy-Anemia Subscale was developed to evaluate symptoms of anemia in patients receiving cancer therapy.[12] Higher scores indicate lower burden of symptoms. FACT-AnS has also been used to assess health status in other chronic illnesses like chronic kidney disease and heart failure.[16,26]

### Statistical analysis

A sample size of 100 subjects was planned to detect a difference in HRQoL score by an effect size of 0.3 in two-tailed test with alpha value of 0.05 and power of 0.8. Clinically important improvement was defined by an increase in HRQoL score by more than one-half standard deviation (SD).[27,28] The intended sample size enabled detection of change in HRQoL with a smaller effect size.

PCS, MCS, and FACT-AnS scores on Days 1 and 7 were respectively compared with the baseline values on Day 0 by paired t tests. Effect size was calculated by the standardized response mean.[28]

Multiple linear regression analysis with enter method was performed to identify factors associated with the change in PCS, MCS, and FACT-AnS scores on Days 1 and 7 from their respective baseline values on Day 0. Predictor variables of interest were transfusion trigger and number of RBC units administered on Day 0. Potential confounders including number of RBC units transfused in the past 1 week before recruitment and number of RBC units transfused during Day 1 to Day 7 were adjusted. Univariate analysis was performed to explore for potential association of age, sex, CCI, admission status, and HRQoL score on Day 0 with PROs. Variables were included in multiple linear regression if their alpha values were less than 0.1 in univariate analysis.[29] Multicollinearity diagnostics was performed by measuring the variable inflation factors of predictors.

In addition to linear regression analysis, we assessed the relationship between patients' characteristics and clinically important improvement in HRQoL with t tests and chi-square tests for continuous and categorical variables respectively. Mann-Whitney U test or Fisher's exact tests were used instead if the assumptions of parametric tests were violated.

We calculated the correlation coefficients of the change in HRQoL scores and physical variables. These variables included the Hb levels on Days 1 and 7, the change in MEWS, and the length of hospital stay of inpatients.

Full missing score estimation was used to calculate PCS and MCS scores when there were missing items.[30] Prostration was performed to obtain FACT-AnS if the number of the missing items was less than 50%.[12] Available case analysis was adopted to deal with missing data.

Computer software (R version 3.3.0, https://cran.r-project.org/bin/windows/base/old/3.3.0/) was used in statistical analysis. p values of less than 0.05 were regarded as significant unless otherwise specified.

## RESULTS

We recruited 101 patients during the study period. HRQoL instruments were administered to all participants on Day 0. Two of them were excluded in data analysis because they had bleeding symptoms during the follow-up period. In the remaining 99 patients, HRQoL questionnaires were completed by 95 and 78 of them on Days 1 and 7, respectively.

Subjects' baseline characteristics and the transfusion therapy they received are summarized in Table 1. The mean (±SD) age of the study population was 63.7 (±13.4) years. There were 59 male patients (60%). Sixty-five patients (66%) received transfusion as inpatients. Sixteen patients (16%) scored 0 in CCI. The comorbidity burden was mild (CCI 1-2) in 46 patients (46%), moderate (CCI 3-4) in 20 (20%), and high (CCI 5 or higher) in 17 (17%). Common comorbid medical conditions included cancer and leukemia (n = 49, 49%), diabetes mellitus (n = 22, 22%), myocardial infarction or congestive heart failure (n = 13, 13%), and moderate to severe renal disease (n = 21, 21%). The majority of patients had chronic anemia (n = 82, 83%) and the most common cause was hematologic disease (n = 40, 40%). More than half of the patients had acute anemia (n = 57, 58%). RBC transfusion was given to 32 patients (32%) in the week before recruitment. The transfusion trigger was less than 70 g/L in 32 patients (32%), between 70 and 79 g/L in 50 (51%), and 80 g/L or more in 17 (17%). One unit of RBC was transfused to 54 patients (55%) and 2 units or more were transfused to 45 patients (45%) on Day 0.

Table 2 shows the change in HRQoL scores on Days 1 and 7 from the baseline values on Day 0. The mean PCS score of the participants did not change on Day 1 ($p = 0.139$); it increased with a small effect size on Day 7 ($p = 0.048$, ES = 0.23). The mean MCS score did not change significantly during the follow-up period ($p = 0.784$ and 0.378 on Days 1 and 7, respectively). The mean FACT-AnS score increased on Day 1 ($p < 0.001$, ES = 0.41) and Day 7 ($p < 0.001$, ES = 0.38) but the effect sizes were small.

The change in HRQoL scores of individual patients after blood transfusion is illustrated in Fig. 1. PCS score improved in 53 (56%) and 44 patients (57%) on Days 1 and 7; the improvement was clinically important in 35 (37%) and 30 patients (39%) on Days 1 and 7, respectively. MCS score improved in 44 (46%) and 40 patients (52%) on Days 1 and 7; clinically significant improvement was observed in 31 (33%) and 27 patients (35%) on Days 1 and 7, respectively. FACT-AnS score was higher than baseline value in 67 (71%) and 53 patients (68%) on Days 1 and 7;

**TABLE 1. Patients' characteristics (n = 99)***

| | |
|---|---|
| Male | 59 (60) |
| Age (years) | 63.7 ± 13.4 |
| Admission status | |
| Outpatient | 34 (34) |
| Inpatient | 65 (66) |
| Received RBC transfusion within past 1 week | 32 (32) |
| CCI | 2 (2-4) |
| Comorbidity | |
| Myocardial infarction or congestive heart failure | 13 (13) |
| Diabetes mellitus | 22 (22) |
| Moderate or severe renal disease | 21 (21) |
| Moderate or severe liver disease | 9 (9) |
| Cancer and leukemia | 49 (49) |
| Depression | 2 (2) |
| History of chronic anemia | 82 (82) |
| Etiology of chronic anemia | |
| Hematological disease | 40 (40) |
| Chronic renal failure (eGFR < 30 mL/min) | 18 (18) |
| Liver cirrhosis | 4 (4) |
| Iron deficiency anemia | 13 (13) |
| Anemia of chronic illness | 17 (17) |
| Miscellaneous or unknown | 7 (7) |
| Acute anemia | 57 (58) |
| Etiology of acute anemia | |
| Recent blood loss | 20 (20) |
| Hemodilution | 10 (10) |
| Sepsis or inflammatory disease | 13 (13) |
| Use of cytotoxic drugs | 14 (14) |
| Miscellaneous or unknown | 9 (9) |
| Transfusion trigger (g/L) | 72 (66-78) |
| Number of RBC unit(s) administered on Day 0 | |
| 1 | 54 (55) |
| 2 | 43 (43) |
| 3 or more | 2 (2) |

* Data are reported as number (%), mean ± SD, or median (IQR).
eGFR = estimated glomerular filtration rate.
Range of transfusion trigger: 36-88 g/l.

**TABLE 2. Change in HRQoL scores from Day 0**

| | Day 1 (n = 95) | | | Day 7 (n = 78†) | | |
|---|---|---|---|---|---|---|
| HRQoL scale | Δ | p value | Effect size | Δ | p value | Effect size |
| PCS | 2.6 | 0.14 | 0.15 | 3.8 | 0.05* | 0.23 |
| MCS | 0.5 | 0.78 | 0.03 | 1.9 | 0.38 | 0.10 |
| FACT-AnS | 4.3 | <0.01* | 0.41 | 4.8 | <0.01* | 0.38 |

* $p < 0.05$.
† PCS and MCS scores were available in 77 subjects on Day 7.
Δ = change in HRQoL scores.

the increase was above the threshold of clinically important improvement in 35 (37%) and 35 patients (45%) on Days 1 and 7, respectively.

The effect of transfusion prescription and other factors on PROs was determined by multiple linear regression analysis. The results are illustrated in Table 3. Transfusion trigger and number of RBC units transfused on Day 0 were not associated with the change in HRQoL across all the scales on Days 1 and 7. Worse baseline scores on Day 0 were associated with greater improvement in PROs on Days 1 and 7 ($p < 0.001$ for the change in PCS, MCS, and FACT-AnS scores on both Day 1 and Day 7). Outpatient transfusion was a significant predictor of HRQoL improvement on Day 1 ($p = 0.037$, $p = 0.013$, and $p < 0.001$ for the change in PCS, MCS, and FACT-AnS scores, respectively) but not on Day 7 ($p = 0.209$, $p = 0.135$, and $p = 0.334$ for the change in PCS, MCS, and FACT-AnS scores, respectively).

Tables 4 and 5 show the relationship between patients' characteristics and clinically important improvement in HRQoL. Patients with acute anemia were less likely to have clinically important improvement in FACT-AnS on Day 1 ($p = 0.017$). On Day 7, an association was found between hematologic disease and clinically important improvement in MCS ($p = 0.028$) and between anemia of chronic illness and clinically important improvement in FACT-AnS ($p = 0.029$). Other demographic factors had no significant association with clinically important improvement in HRQoL.

We analyzed the correlation between the change in HRQoL and physical variables (Table 6). Hb levels were available in 58 patients and 48 patients on Days 1 and 7, respectively. The mean Hb level increased by 19 g/L (95% confidence interval [CI],16-22 g/L) on Day 1 and 17 g/L (95% CI, 14-21 g/L) on Day 7. On Day 1, Hb level had a positive correlation with the change in PCS score ($p = 0.012$), but not with the change in MCS ($p = 0.811$) and FACT-AnS scores ($p = 0.858$). Hb level did not correlate with the change in HRQoL on Day 7. The vast majority of inpatients had MEWS of 0 (n = 52 [82%] on Day 0; n = 53 [82%] on Day 1), meaning that all physiologic variables were within normal limits in these patients. Therefore, we did not perform correlation analysis of the change in MEWS and HRQoL. The median (IQR) length of hospital stay was 8 (5-19) days in participants receiving RBC transfusion during inpatient care. There was no correlation between the length of hospital stay and the change in HRQoL on Day 7 ($p = 0.100$, $p = 0.785$, and $p = 0.353$ for the change in PCS, MCS, and FACT-An scores, respectively).

Patients receiving a single-unit transfusion were more likely to require another transfusion during Day 1 to Day 7 than those receiving 2 or more units of RBC on Day 0 (46% vs. 13%, $p < 0.001$). Nevertheless, the average RBC requirement in 1 week was 0.6 units less in patients transfused with a single unit of RBCs on Day 0 ($p < 0.001$). Transfusion-related complications occurred in five patients (5%). All were self-limiting events. The baseline characteristics of patients who did not complete the HRQoL instruments during the follow-up period were comparable to the remaining participants.

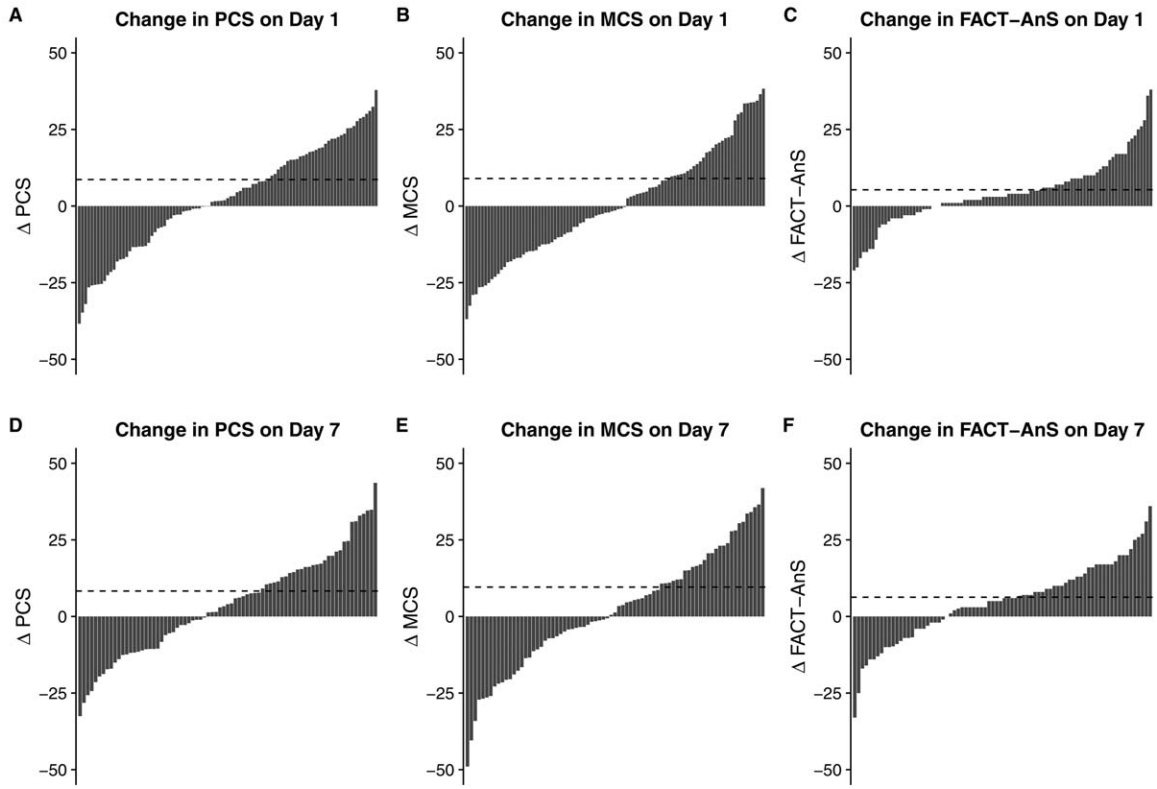


**Fig. 1. The change in HRQoL scores over time. Waterfall plots showing the difference in PCS, MCS, and FACT-AnS scores on Day 1 and Day 7 from baseline values. Dashed lines represent the threshold of clinically important difference. Δ = change in HRQoL scores.**

**TABLE 3. Multiple linear regression analysis with difference in HRQoL scores from baseline values as dependent variables**

| | $\beta_{adj}$† | (95% CI) | $\beta_{adj}$ | (95% CI) | $\beta_{adj}$ | (95% CI) |
|---|---|---|---|---|---|---|
| Factors affecting PRO | Δ PCS on Day 1 (n = 95) | | Δ MCS on Day 1 (n = 95) | | Δ FACT-AnS on Day 1 (n = 95) | |
| Number of RBC units transfused on Day 0 | 4.4 | (–0.7 to 9.6) | –0.8 | (–6.0 to 4.3) | 0.9 | (–3.1 to 5.0) |
| Transfusion trigger | 0.8 | (–1.9 to 3.5) | –0.3 | (–3.0 to 2.5) | 0.2 | (–1.9 to 2.3) |
| Number of RBC units received in past 1 week | –1.7 | (–4.1 to 0.8) | –1.0 | (–3.3 to 1.4) | –1.5 | (–3.4 to 0.3) |
| Outpatient | 5.9* | (0.4 to 11.4) | 7.0* | (1.5 to 12.5) | 7.6* | (3.2 to 11.9) |
| HRQoL score on Day 0 | –1.0* | (–1.2 to –0.8) | –1.0* | (–1.2 to –0.8) | –0.3* | (–0.4 to –0.1) |
| | Δ PCS on Day 7 (n = 77) | | Δ MCS on Day 7 (n = 77) | | Δ FACT-AnS on Day 7 (n = 78) | |
| Number of RBC units transfused on Day 0 | 3.7 | (–3.0 to 10.3) | –1.2 | (–8.1 to 5.7) | 2.2 | (–3.9 to 8.2) |
| Transfusion trigger | –1.5 | (–5.0 to 2.0) | –1.9 | (–5.5 to 1.8) | –2.1 | (–5.3 to 1.1) |
| Number of RBC units received in past 1 week | –0.5 | (–4.1 to 3.1) | 1.0 | (–2.7 to 4.7) | –0.8 | (–4.0 to 2.5) |
| Number of RBC units received during Days 1-7 | –2.1 | (–5.9 to 1.8) | 0.2 | (–3.9 to 4.3) | –1.5 | (–5.1 to 2.1) |
| Outpatient | 4.2 | (–2.4 to 10.8) | 5.2 | (–1.7 to 12.1) | 3.0 | (–3.1 to 9.1) |
| HRQoL score on Day 0 | –0.9* | (–1.2 to –0.7) | –1.1* | (–1.3 to –0.8) | –0.3* | (–0.5 to –0.2) |

* $p < 0.05$.
† Adjusted regression coefficients in multiple linear regression analysis.
Δ = change in HRQoL score.

**TABLE 4. Patients' characteristics and clinically important improvement in HRQoL (Day 1)***

| | CID in PCS (Day 1) | | | | | CID in MCS (Day 1) | | | | | CID in FACT-AnS (Day 1) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients' characteristics | Yes | | No | | p value | Yes | | No | | p value | Yes | | No | | p value |
| Number of patients | 35 | (37) | 60 | (63) | | 31 | (33) | 64 | (67) | | 35 | (37) | 60 | (63) | |
| Male | 22 | (63) | 35 | (58) | 0.83 | 19 | (61) | 38 | (59) | 1.00 | 15 | (43) | 23 | (38) | 0.82 |
| Age (years) | 60.7 | ± 14 | 66 | ± 12 | 0.07 | 64 | ± 11 | 64 | ± 14 | 0.94 | 66 | ± 13 | 63 | ± 13 | 0.20 |
| Received RBC transfusion within past 1 week | 10 | (29) | 21 | (35) | 0.68 | 10 | (32) | 21 | (33) | 1.00 | 7 | (20) | 24 | (40) | 0.08 |
| CCI | 2 | (2-4) | 2 | (2-4) | 0.88 | 2 | (2-5) | 2 | (1-3) | 0.17 | 2 | (1-4) | 2 | (2-4) | 0.60 |
| Comorbidity | | | | | | | | | | | | | | | |
| Myocardial infarction or congestive heart failure | 4 | (11) | 9 | (15) | 0.86 | 4 | (13) | 9 | (14) | 1.00 | 6 | (17) | 7 | (12) | 0.66 |
| Diabetes mellitus | 8 | (23) | 14 | (23) | 1.00 | 8 | (26) | 14 | (22) | 0.86 | 7 | (20) | 15 | (25) | 0.76 |
| Moderate or severe renal disease | 10 | (29) | 11 | (18) | 0.37 | 8 | (26) | 13 | (20) | 0.73 | 6 | (17) | 15 | (25) | 0.53 |
| Moderate or severe liver disease | 3 | (9) | 6 | (10) | 1.00 | 3 | (10) | 5 | (8) | 1.00 | 3 | (9) | 5 | (8) | 1.00 |
| Cancer and leukemia | 17 | (49) | 31 | (52) | 0.94 | 20 | (65) | 28 | (44) | 0.09 | 17 | (49) | 31 | (52) | 0.94 |
| History of chronic anemia | 31 | (89) | 47 | (78) | 0.33 | 26 | (84) | 52 | (81) | 0.98 | 30 | (86) | 48 | (80) | 0.67 |
| Etiology of chronic anemia | | | | | | | | | | | | | | | |
| Hematologic disease | 13 | (37) | 25 | (42) | 0.83 | 16 | (39) | 22 | (34) | 0.17 | 14 | (40) | 24 | (40) | 1.00 |
| Chronic renal failure (eGFR < 30 mL/min) | 9 | (26) | 9 | (15) | 0.31 | 7 | (23) | 11 | (17) | 0.73 | 5 | (14) | 13 | (22) | 0.54 |
| Liver cirrhosis | 3 | (9) | 0 | (0) | 0.09 | 2 | (6) | 1 | (2) | 0.51 | 1 | (3) | 2 | (3) | 1.00 |
| Iron deficiency anemia | 4 | (11) | 8 | (13) | 1.00 | 2 | (6) | 10 | (16) | 0.35 | 3 | (9) | 9 | (15) | 0.56 |
| Anemia of chronic illness | 8 | (23) | 9 | (15) | 0.49 | 5 | (16) | 12 | (19) | 0.98 | 10 | (29) | 7 | (12) | 0.07 |
| Acute anemia | 17 | (49) | 40 | (67) | 0.13 | 15 | (48) | 42 | (66) | 0.17 | 15 | (43) | 42 | (70) | 0.02† |
| Etiology of acute anemia | | | | | | | | | | | | | | | |
| Recent blood loss | 4 | (11) | 10 | (17) | 0.77 | 4 | (13) | 16 | (25) | 0.28 | 4 | (11) | 16 | (27) | 0.13 |
| Hemodilution | 7 | (20) | 3 | (5) | 0.90 | 0 | (0) | 10 | (16) | 0.05 | 2 | (6) | 8 | (13) | 0.41 |
| Sepsis or inflammatory disease | 2 | (6) | 11 | (18) | 0.16 | 4 | (13) | 9 | (14) | 1.00 | 3 | (9) | 10 | (17) | 0.42 |
| Use of cytotoxic drugs | 5 | (14) | 9 | (15) | 1.00 | 6 | (19) | 8 | (13) | 0.57 | 5 | (14) | 9 | (15) | 1.00 |

* Data are reported as number (%), mean ± SD, or median (IQR).
† $p < 0.05$.
CID = clinically important difference; eGFR = estimated glomerular filtration rate.

## DISCUSSION

### The change in health status after RBC transfusion

We evaluated the change in health status after RBC transfusion with generic and anemia symptom-specific scales in this study. Generic HRQoL was assessed with the acute form of SF-12v2. The mean PCS score of the participants improved on Day 7 but the effect size was small. The mean PCS score on Day 1 and the mean MCS scores on Days 1 and 7 did not change significantly after RBC transfusion. The waterfall plots in Fig. 1 illustrate that the change in PCS and MCS scores was heterogeneous. PCS and MCS scores improved in 46% to 57% of patients and clinically important improvement was achieved by 33% to 39% of patients during the follow-up period. The heterogeneity of response could be explained by the diversity of the study population. Participants had variable comorbidity burden with 37% of them scoring 3 or more on the CCI. It is not surprising that a considerable proportion of patients had moderate to severe comorbidity burden because the study population was general medical patients. Moreover, hospitalized patients were admitted for various reasons and anemia could be only one of the active problems. They may have received interventions other than RBC transfusion during the study period. SF-12v2, as a generic measure of HRQoL, is not specific to symptoms of anemia. All these factors could account for the heterogeneous change in PCS and MCS scores after RBC transfusion.

FACT-AnS is more responsive to concerns related to anemia and fatigue than generic HRQoL instruments.[31] The mean FACT-AnS score of the participants increased significantly by an effect size 0.41 and 0.38 on Days 1 and 7, respectively. The threshold of clinically important difference was not reached. However, one-half SD is only a conservative estimate of clinically important difference and effect sizes below that may still be meaningful.[28] The FACT-AnS score improved in 68% to 71% of patients after blood transfusion and the improvement was clinically important in 37% to 45% of patients. Our findings suggest that RBC transfusion relieves symptoms of anemia in some medical patients.

### Factors affecting PROs after RBC transfusion

As discussed earlier, the study population responded heterogeneously to RBC transfusion. It is essential to

**TABLE 5. Patients' characteristics and clinically important improvement in HRQoL (Day 7)***

| | CID in PCS (Day 7) | | | | | CID in MCS (Day 7) | | | | | CID in FACT-AnS (Day7) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Patients' characteristics | Yes | | No | | p value | Yes | | No | | p value | Yes | | No | | p value |
| Number of patients | 30 | (39) | 47 | (61) | | 27 | (35) | 50 | (65) | | 35 | (45) | 43 | (55) | |
| Male | 13 | (43) | 20 | (43) | 1.00 | 10 | (37) | 23 | (46) | 0.60 | 14 | (40) | 19 | (44) | 0.88 |
| Age (years) | 62 | ± 13 | 65 | ± 12 | 0.23 | 66 | ± 12 | 63 | ± 12 | 0.29 | 65 | ± 11 | 63 | ± 13 | 0.38 |
| Received RBC transfusion within past 1 week | 7 | (23) | 20 | (43) | 0.14 | 10 | (37) | 17 | (34) | 0.99 | 8 | (23) | 19 | (44) | 0.08 |
| CCI | 2 | (2-3) | 2 | (2-4) | 0.21 | 2 | (2-4) | 2 | (2-4) | 0.41 | 2 | (1-5) | 2 | (2-4) | 0.88 |
| Comorbidity | | | | | | | | | | | | | | | |
| Myocardial infarction or congestive heart failure | 4 | (13) | 5 | (11) | 1.00 | 5 | (19) | 4 | (8) | 0.32 | 5 | (14) | 4 | (9) | 0.74 |
| Diabetes mellitus | 8 | (27) | 8 | (17) | 0.47 | 3 | (11) | 13 | (26) | 0.21 | 7 | (20) | 9 | (21) | 1.00 |
| Moderate or severe renal disease | 4 | (13) | 11 | (23) | 0.43 | 7 | (26) | 8 | (16) | 0.45 | 3 | (9) | 12 | (28) | 0.06 |
| Moderate or severe liver disease | 3 | (10) | 6 | (13) | 1.00 | 3 | (11) | 6 | (12) | 1.00 | 5 | (14) | 4 | (9) | 0.72 |
| Cancer and leukemia | 16 | (53) | 28 | (60) | 0.76 | 19 | (70) | 25 | (50) | 0.14 | 18 | (51) | 27 | (63) | 0.44 |
| History of chronic anemia | 24 | (80) | 40 | (85) | 0.79 | 25 | (93) | 39 | (78) | 0.19 | 29 | (83) | 36 | (84) | 1.00 |
| Etiology of chronic anemia | | | | | | | | | | | | | | | |
| Hematologic disease | 12 | (40) | 22 | (47) | 0.73 | 17 | (63) | 17 | (34) | 0.03† | 13 | (37) | 22 | (51) | 0.31 |
| Chronic renal failure (eGFR < 30 mL/min) | 3 | (10) | 9 | (19) | 0.45 | 6 | (22) | 6 | (12) | 0.39 | 3 | (9) | 9 | (21) | 0.23 |
| Liver cirrhosis | 2 | (7) | 2 | (4) | 1.00 | 2 | (7) | 2 | (4) | 0.92 | 3 | (9) | 1 | (2) | 0.47 |
| Iron deficiency anemia | 3 | (10) | 6 | (13) | 1.00 | 2 | (7) | 7 | (14) | 0.63 | 3 | (9) | 6 | (14) | 0.70 |
| Anemia of chronic illness | 6 | (20) | 9 | (19) | 1.00 | 3 | (11) | 12 | (24) | 0.29 | 11 | (31) | 4 | (9) | 0.03† |
| Acute anemia | 18 | (60) | 30 | (64) | 0.92 | 14 | (52) | 45 | (90) | 0.25 | 20 | (57) | 28 | (65) | 0.63 |
| Etiology of acute anemia | | | | | | | | | | | | | | | |
| Recent blood loss | 5 | (17) | 9 | (19) | 1.00 | 2 | (7) | 12 | (24) | 0.14 | 8 | (23) | 6 | (14) | 0.47 |
| Hemodilution | 2 | (7) | 7 | (15) | 0.46 | 1 | (4) | 8 | (16) | 0.22 | 1 | (3) | 8 | (19) | 0.07 |
| Sepsis or inflammatory disease | 3 | (10) | 8 | (17) | 0.60 | 3 | (11) | 8 | (16) | 0.80 | 4 | (11) | 7 | (16) | 0.78 |
| Use of cytotoxic drugs | 5 | (17) | 8 | (17) | 1.00 | 7 | (26) | 6 | (12) | 0.22 | 5 | (14) | 8 | (19) | 0.84 |

* Data are reported as number (%), mean ± SD, or median (IQR).
† $p < 0.05$.
CID = clinically important difference; eGFR = estimated glomerular filtration rate.

**TABLE 6. Correlation analysis of Hb level and length of hospital stay with PROs**

| | Difference in HRQoL scores from baseline values on Day 0 | | | | | |
|---|---|---|---|---|---|---|
| Outcome parameters | *r* | p value | *r* | p value | *r* | p value |
| | Δ PCS (Day 1), n = 58 | | Δ MCS (Day 1), n = 58 | | Δ FACT-AnS (Day 1), n = 58 | |
| Hb on Day 1 | 0.33 | 0.01* | –0.03 | 0.81 | –0.02 | 0.86 |
| | Δ PCS (Day 7), n = 44 | | Δ MCS (Day 7), n = 44 | | Δ FACT-AnS (Day 7), n = 45 | |
| Hb on Day 7 | 0.19 | 0.23 | –0.05 | 0.73 | 0.12 | 0.43 |
| | Δ PCS on Day 7, n = 52 | | Δ MCS on Day 7, n = 52 | | Δ FACT-AnS on Day 7, n = 52 | |
| Length of hospital stay in inpatients | –0.23 | 0.10 | 0.04 | 0.79 | –0.13 | 0.35 |

* $p < 0.05$.
Δ = change in HRQoL score.

determine the predictors of PROs, which could have implications for transfusion practice. A multiple linear regression analysis with the change in HRQoL scores as dependent variables was performed. Lower baseline HRQoL scores before transfusion were associated with greater improvement in PROs across all the scales. It suggests that RBC transfusion probably has greater benefit to more symptomatic patients. Transfusion trigger and number of RBC units administered had no significant association with the change in HRQoL. This provides evidence against using Hb level as the only indicator to make transfusion decisions. Thorough clinical assessment could avoid unnecessary transfusion in asymptomatic patients. Patients receiving single-unit transfusion on Day 0 on average consumed 25% less RBC units during the 1-week follow-up period. The single-unit transfusion policy

potentially reduces overall blood use without jeopardizing PROs.

Blood transfusion as an outpatient was associated with better PROs on Day 1, but the beneficial effect disappeared on Day 7. In comparison to outpatients, hospitalized patients were more likely to have comorbid medical conditions and receive interventions other than RBC transfusion. These factors could influence the change in HRQoL. The median (IQR) length of stay was 8 (5-19) days in participants receiving transfusion during inpatient care. Almost half of them were medically fit for discharge on Day 7. Therefore, their improvement in HRQoL was able to catch up with the outpatient transfusion recipients in 1 week's time.

The need to consider the characteristics of individual patients in every transfusion decision cannot be emphasized enough. We therefore evaluated if patients' demographics, comorbidity profiles, and etiologies of anemia were associated with clinically important improvement in HRQoL after blood transfusion. Clinically important improvement in one of the HRQoL scales on either Day 1 or Day 7 was observed in patients without acute anemia and patients with hematologic disease or anemia of chronic illness. However, the associations were not consistent in other HRQoL scales and at different time points that we could not conclude if these factors modified PROs.

### Strengths and weaknesses

The noninferiority of restrictive transfusion practice has been demonstrated by past studies using physical variables as outcome measures.[5,6,32,33] There is a dearth of knowledge regarding the relationship between RBC transfusion and PROs. In our analysis, restrictive transfusion threshold and single-unit policy did not adversely affect the change in HRQoL after RBC transfusion. The results are complementary to current evidence because restrictive transfusion is now supported by quality-of-life research as well. Moreover, transfusion practice was mainly assessed in critical care or postoperative patients in the past. Our findings provide direct evidence to extend the recommendations for restrictive transfusion to general medical patients.

The significance of the variables in multiple linear regression analysis was consistent in all the HRQoL scales. Generic HRQoL measures consider the effect of comorbidity and allow comparison across different patient categories. FACT-AnS, on the other hand, is more specific to symptoms of anemia and the effect of RBC transfusion.[31,34] The consistency of our findings strengthen the explanatory power of the predictors.

There are certain limitations in the study. The posttransfusion Hb levels were available in approximately half of the patients only. Although the posttransfusion Hb level was positively correlated with the improvement in PCS on Day 1, it has no correlation with other HRQoL scales. We could not conclude if the improvement in HRQoL was related to Hb concentration increment.

We did not recruit patients who received RBC transfusion after hours. These patients might have different characteristics and response to transfusion from our study population. This could result in selection bias. The generalizability of our findings is also limited by excluding some groups of patients. Unstable or cognitively impaired patients were excluded because they were not able to complete the HRQoL instruments. Patients with a transfusion-dependent condition or ongoing bleeding have different transfusion requirements that it is not suitable to include them in this study.

The decision to transfuse is often complex. It is affected by patients' factors like Hb level, age, symptoms, and etiology of anemia. Doctors' belief and availability of alternative treatments like EPO-stimulating agents would also influence transfusion decisions. We studied the effect of transfusion trigger and number of RBC units transfused on PROs with linear regression. Although we controlled for recent transfusion requirements, unmeasured confounders could lead to biased effect estimates in this observational study. Confounding may also distort the results when we assessed the relationship between patients' characteristics and clinically important difference in HRQoL. Moreover, we did not examine the effect of interactions in regression analysis because of the limited sample size. Randomized controlled trials including PROs as one of the outcome measures could enhance our understanding to the optimal transfusion strategy. Increasing the sample size in future studies and evaluating the effect of interactions would be helpful to improve the precision in transfusion practice.

In conclusion, PROs after RBC transfusion in medical patients were heterogeneous. HRQoL scale specific to symptoms of anemia improved in most of the patients but less than half of them had clinically important improvement. RBC transfusion was more beneficial to patients with worse baseline HRQoL scores. Transfusion as outpatient was associated with better PROs but the advantageous effect disappeared on Day 7. Transfusion trigger and number of RBC units administered were not associated with the change in HRQoL. Our findings support the practice of restrictive transfusion and single-unit policy. Careful assessment of anemia symptoms instead of solely relying on Hb level to make transfusion decisions could avoid unnecessary RBC transfusion.

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### CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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