Association of preoperative red blood cell width and postoperative 30-day mortality in patients undergoing non-cardiac surgery: a retrospective cohort study using propensity-score matching Running title: The association between RDW and postoperative 30-day mortality

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Abstract

Background: In terms of predicting surgery mortality, it is controversial whether red blood cell width works independently. In non-cardiac surgery patients older than 18 years, we intend to examine the relationship between red blood cell width and postoperative 30-day mortality.

Methods: In this retrospective cohort study, 90,785 Singapore General Hospital patients were matched by propensity score between January 1, 2012 and October 31, 2016. It was determined that red blood cell width at baseline and mortality within 30 days after surgery were the independent and dependent variables. We used a non-parametric multivariate logistic regression to balance the confounders among 7807 patients with high RDW and 7807 patients with non-high RDW in the propensity score matching. We investigated the association between RDW and 30-day mortality after surgery using the doubly robust estimation method.

Results: Cohorts matched according to propensity score, the risk of 30-day mortality after surgery increased by 114.6.0% among high RDW group(OR = 2.146, 95%CI: 1.645−2.799, P 0.00001). In crude model, there was a significant correlation between RDW and 30-day mortality after surgery (OR = 1.877, 95% CI: 1.476−2.388, P 0.00001). In the propensity-score adjusted model, the risk of 30-day mortality after surgery dropped to 86.7% among people with high RDW (OR = 1.867, 95%CI: 1.467−2.376,P 0.00001).Compared to non-high RDW group, the risk of 30-day mortality after surgery increased by 117.0% and 127.7% among high RDW group in the original cohort(OR: 2.170, 95%CI: 1.754−2.683, P 0.00001) and the weighted cohort(OR: 2.272, 95%CI: 2.009−2.580, P 0.00001),respectively.

Conclusions: According to the results of this observational, propensity score-matched cohort study, there is a significant correlation between higher RDW and higher postoperative 30-day mortality, that is to say, patients over the age of 18 with high preoperative RDW who undergo non-cardiac surgery have a worse postoperative prognosis than those with normal RDW.

Background

Surgery plays a crucial role in global health care. The perioperative mortality rate is estimated to be as high as 0.8-4% (1). In addition to the major complications induced by anesthesia and surgery, perioperative mortality is mainly negatively affected by individual patient comorbidities. Therefore, whether we can find a simple, cheap and easily accessible index to predict perioperative mortality, help surgeons to do perioperative evaluation, so as to reduce the incidence of surgical mortality and serious complications has become a problem to be solved in modern surgery.

The normal range for Red blood cell width(RDW)is 11.0−15.0% (2). The larger the value, the greater the difference in red blood cell volume. When the RDW value is significantly increased, it often indicates red blood cell debris, different sizes, red blood cell polymorphism, or increased reticulocytes. Traditionally, RDW is commonly used in the diagnosis or differential diagnosis of hematological diseases (3, 4), but

now it has shown to be important for predicting the prognosis of some diseases, including cardiovascular disease (5, 6), kidney disease (7, 8), liver disease (9).

Whether RDW is associated with surgical mortality and whether it can be used as an independent predictor of surgery is currently controversial. A study by Davide Lazzeroni et al (10) demonstrated that RDW was a reliable predictor of total mortality and cardiovascular mortality in cardiac revascularization and cardiopulmonary bypass patients. Similarly, Pluta M et al (11) showed that RDW is a valuable screening predictor of hospitalized mortality in patients with high risk gastrointestinal surgery Abdullah et al.'s (12) research further clarified risk of increased 30 day mortality after preoperative RDW independence.

However, Cheung YN et al. (13) found that although preoperative RDW can independently predict the acceptance of large or ultra large non- cardiac surgery, the 30-day mortality rate of surgical patients may not be a useful prognostic indicator due to their low sensitivity and specificity. An analysis of studies by Shota S et al. (14) revealed that preoperative RDW was not an independent prognostic indicator of overall survival (OS) which be used in patients with gastric adenocarcinoma. The study of Pedrazzani C et al. (15) also showed that preoperative H-RDW was not an independent prognostic factor for cancer patients.

The propensity score(PS)indicates the probability that each observation result is assigned to the treatment group if all variables observed in clinical study exist. Observational clinical studies can synthesize all known observed variables through propensity score values, and then balance treatment and control group observations by propensity score matching, stratification, regression adjustment, weighting, etc. The distribution of variables, thereby reducing bias and increasing the comparability of the two groups. The use of propensity scores by researchers can allow observational clinical studies to achieve post-hoc randomization without over-stratification and over-matching, so that the research results are closer to the "real world" actual intervention effects. As a new method of balancing observed variables, propensity score method is widely used in the study of observational and clinical non-randomized data. This method treats each propensity score as an independent variable whose distribution is randomized to achieve a study effect similar to that of a randomized controlled trial (RCT) with minimal bias. Therefore, this study employed PSM analysis to explore whether there is an association between RDW and perioperative mortality.

Methods

Study design and data source

This study was based on a secondary analysis of a single center retrospective study at Singapore general hospital from Jan 1, 2012 to October, 1700 beds grade three academic hospital. We downloaded the raw data for free from the DATADRYAD database (www.datadryad.org). Since Diana Xin Hui Chan et al. transferred the ownership of the original data to the DATADRYAD website, we were able to use these data to perform secondary data analysis based on different scientific assumptions (Dryad data package:

In accordance with all relevant guidelines and regulations, the Singapore Health Institutional Review Board (Singhealth CIRB 2014/651/D) approved the study prior to the start of the experiment. A paper published in the journal described the ethical approval process (17).

Study sample

Study participants included 100,873 surgical patients in total. Baseline exclusion criteria for the original study were as follows : (1) In cardiac surgery, burn-related surgery, neurosurgery, and transplantation, patients are categorically more likely to die as a result of intensive blood transfusion requirements, as well as their substantially higher mortality rates ; (2) There is no information available about RDW; (3) Under 18 years old. A diagram in Fig. 1 shows the process of selecting participants. A secondary analysis of 84,547 participants was conducted .

Exposure and outcome

The primary exposure of interest was RDW. In red blood cell volume, RDW is the variance of red blood cell volume compared to a normal reference range. In the laboratory of this hospital, normally, RDW ranges from 10.9–15.7%, with levels above 15.7% classified as high (16). On the basis of the cut-off value of 15.7%, 39.5% of the population was regarded as sensitive, 89.3% as specific, 5.3% as positive, and 99.0% as negative (18).

After their index operation, patients were followed up for 30 days to determine if any mortality occurred. An electronic health record synchronization with the mortality data was carried out to ensure near-complete follow-up (16).

Covariates

As a result of clinical experience and previous research, we identified potential confounders a priori that may affect the relationship between RDW and perioperative prognosis in our study. During the preoperative anesthetic assessment, the following data were included age, gender, race, preoperative estimated glomerular filtration rate (eGFR),presence of cerebrovascular accidents (CVA), diabetes mellitus (DM),ischemic heart disease (IHD),congestive heart failure (CHF), anemia, priority of surgery, anesthesia type, surgical risk, preoperative blood transfusion with in 30days, intraoperative blood transfusion data, postoperative blood transfusion data, the Revised Cardiac Risk Index (RCRI) score (19), the ASA status,ICUADMGT24H. Preoperative laboratory results including renal group (including eGFR) and full blood count (including hemoglobin concentration) were taken as the latest blood results within 90 days before surgery, and up to the day of surgery. The severity of anemia was defined by WHO's gender-based classification of hemoglobin concentration. Mild anemia was defined as hemoglobin concentration of 11–12.9g/dL in males and 11–11.9g/dL in females; moderate anemia was defined for both genders to

be hemoglobin concentration between 8–10.9g/dL and severe anemia defined as hemoglobin concentration between 8–10.9g/dL and severe anemia defined as hemoglobin concentration < 8.0g/dL. Priority of surgery (emergency or elective) and surgical risk classification were based on the 2014 European Society of Cardiology (ESC) and the European Society of Anaesthesiology(ESA) guidelines (20, 21). American Society of Anesthesiologists-Physical Status (ASA-PS) follows that of the ASA-PS definitions (21).In accordance with KDIGO guidelines, the preoperative eGFR was calculated from serum creatinine values using the MDRD Eq. (22).

Statistical analyses

A skewed distribution is represented by medians (quartiles) or means (standard deviations) for continuous variables, and a frequency or percentage was used to express categorical variables. Those variables with normal distribution were tested using two-sample-tests, those with non-normal distribution were tested using Wilcoxon rank-sum tests, and those with categorical distributions were tested using chi-square tests (23). Data with partial missing values can cause confounding in multivariate regression analysis .In the case of categorical variables, the missing data would be treated as a new independent group; in the case of a continuous variable, the missing data will be replaced with an average or median .

Participants in high RDW and non-high RDW groups (Table 1) have different baseline characteristics, based on propensity-score matching (PS), we identified a cohort of patients who shared similar baseline characteristics. An unparsimonious multivariable logistic regression model was used to estimate the propensity score (24), all baseline characteristics highlighted in Table 1 serve as covariates with RDW as the independent variable. In order to match variables, the following were used: age, gender, race, eGFR, CVA, DM, IHD, CHF, ASA status, RCRI score, ICUADMGT24H, anemia, priority of surgery, anesthesia type, surgical risk, preoperative blood transfusion with in 30days, intraoperative blood transfusion data, postoperative blood transfusion data. Matching the samples was performed using a greedy algorithm, with a caliper width of 0.01 using a 1:1 protocol without replacement. Based on all baseline covariates, standardized differences (SD) were calculated to assess imbalance and balance pre- and post-matching (25). It is indicative of a relatively small imbalance when the standard deviation for a given covariate is less than 10.0% (25). RDW and patients' primary and secondary outcomes were also determined using the doubly robust estimation method, which combines multivariate regression with propensity score (26, 27). Using logistic proportional hazards regression, all covariates were adjusted for in the PS-matched cohort .

Table 1
Baseline characteristics before propensity-score matching in the original cohort

RDW	≤ 15.7%	⬜15.7%	Standardize diff.	P-value
N	76069	8478		
AGE(years)	52.84 ± 16.89	53.62 ± 16.84	4.7%	< 0.001
PREOP-EGFR	96.22 ± 31.10	98.29 ± 46.30	5.3%	< 0.001
PS	0.08 ± 0.11	0.32 ± 0.22	135.5%	< 0.001
GENDER			26.6%	< 0.001
Male	36092 (47.45%)	2922 (34.47%)		
Female	39977 (52.55%)	5556 (65.53%)		
Preop-transfusion with in 30days n(%)			28.5%	< 0.001
0 units	74881 (98.44%)	7850 (92.59%)		
1 units	652 (0.86%)	329 (3.88%)		
2 or more units	536 (0.71%)	299 (3.53%)		
Intraop-transfusion			47%	< 0.001
0 units	72806 (95.71%)	6870 (81.03%)		
1 units	3263 (4.29%)	1608 (18.97%)		
Postop-transfusion with in 30days			35%	< 0.001

Values are n (%) or mean ± SD
Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized difffferences;
PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours

RDW	≤ 15.7%	⬚15.7%	Standardize diff.	P-value
0 units	75720 (99.54%)	7885 (93.01%)		
1 units	228 (0.30%)	379 (4.47%)		
2 units	121 (0.16%)	214 (2.52%)		
Anesthesia type n(%)			4.2%	< 0.001
ga	63240 (83.14%)	7178 (84.67%)		
ra	12829 (16.87%)	1300 (15.33%)		
Priority of surgery n(%)			7.9%	< 0.001
Elective	60188 (79.12%)	6430 (75.84%)		
Emergency	15881 (20.88%)	2048 (24.16%)		
Surgical risk			25%	< 0.001
Low	39961 (52.53%)	3553 (41.91%)		
Moderate	33446 (43.97%)	4298 (50.70%)		
High	2662 (3.50%)	627 (7.40%)		
RACE			13.6%	< 0.001
Chinese	54987 (72.29%)	5692 (67.14%)		
Indian	6681 (8.78%)	844 (9.96%)		

Values are n (%) or mean ± SD
Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized difffferences;
PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours

RDW	≤ 15.7%	⃥15.7%	Standardize diff.	P-value
Malay	7324 (9.63%)	1146 (13.52%)		
Others	7077 (9.30%)	796 (9.39%)		
ANEMIA			149.2%	< 0.001
None	59399 (78.09%)	1750 (20.64%)		
Mild	10637 (13.98%)	2053 (24.22%)		
Moderate / Severe	6033 (7.93%)	4675 (55.14%)		
ICUADMGT24H			14.4%	< 0.001
No	75165 (98.81%)	8196 (96.67%)		
Yes	904 (1.19%)	282 (3.33%)		
RCRI.SCORE			33.3%	< 0.001
Level 1	40539 (53.29%)	3432 (40.48%)		
Level 2	10226 (13.44%)	1778 (20.97%)		
Level 3	1923 (2.53%)	462 (5.45%)		
Level 4	648 (0.85%)	223 (2.63%)		
NA	22733 (29.89%)	2583 (30.47%)		
CVA CATEGORY			5.3%	< 0.001

Values are n (%) or mean ± SD
Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized difffferences;
PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours

RDW	≤ 15.7%	⬚15.7%	Standardize diff.	P-value
NO	51180 (67.28%)	5600 (66.05%)		
YES	1299 (1.71%)	205 (2.42%)		
NA	23590 (31.01%)	2673 (31.53%)		
IHD CATEGORY			11%	< 0.001
NO	48760 (64.10%)	5173 (61.02%)		
YES	3522 (4.63%)	602 (7.10%)		
NA	23787 (31.27%)	2703 (31.88%)		
CHF CATEGORY			13.2%	< 0.001
NO	53750 (70.66%)	5779 (68.17%)		
YES	577 (0.76%)	198 (2.34%)		
NA	21742 (28.58%)	2501 (29.50%)		
DM CATEGORY			9.3%	< 0.001
NO	52167 (68.58%)	5625 (66.35%)		
YES	1636 (2.15%)	309 (3.65%)		
NA	22266 (29.27%)	2544 (30.01%)		
ASA CATEGORY			41.5%	< 0.001

Values are n (%) or mean ± SD
Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized difffferences;
PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours

RDW	≤ 15.7%	>15.7%	Standardize diff.	P-value
level I	18383 (24.17%)	1327 (15.65%)		
level II	42568 (55.96%)	4074 (48.05%)		
level III	10677 (14.04%)	2271 (26.79%)		
level IV-VI	730 (0.96%)	335 (3.95%)		
NA	3711 (4.88%)	471 (5.56%)		
Values are n (%) or mean ± SD				
Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized diffferences;				
PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours				

In addition to the estimated propensity score, the inverse probability of treatment weights (IPTW) was calculated. In this study, IPTW was calculated by taking the inverse of propensity score for high RDW patients, as well as the inverse of propensity score for non-high RDW patients (1-propensity score). The weighted cohort was generated using the IPTW model (27). This study included a series of sensitivity analyses designed to assess the robustness of its findings and to examine the impact of various association inference models on our results. In the sensitivity analysis, two association inference models were used, one for the original cohort and one for the weighted cohort. There were p values and effect sizes for all these models reported and compared. According to the STROBE statement, all results are reported (28, 29). Statistical analysis was performed using R software(http://www.R-project.org, The R Foundation) and Empower-Stats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA). Statistical significance was defined as P<0.05 for two-tailed tests.

Results

Study population

We identified 84,547 participates (46.14% men and 53.86% women) who met our inclusion criteria (Fig. 1) of whom 8,478 (10.1%) with high RDW(15.7%) and 76,069 (89.9%) with non-high RDW(≤ 15.7%). Population average age was 52.91 ± 16.88 years. Several baseline characteristics differed between high RDW and non-high RDW groups until propensity-score matching was applied (Table 1). In general, higher RDW was associated with higher risk among patients, such as: RCRI score, Anemia, CV, IHD, CHF, DM, ASA, ICU admission rate. One-to-one matching based on propensity score, 7,807 non-high RDW patients

matched with 7807 high subjects. It is evident from Table 2 that the propensity score was well matched for almost all variables (standard deviations less than 10.0%). As a result, there was only a slight difference in baseline characteristics between non-high RDW and high RDW groups .

Table 2
Baseline characteristics after propensity-score matching in the original cohort

RDW	≤ 15.7%	⬚15.7%	Standardize diff.	P-value
N	7807	7807		
AGE(years)	54.96 ± 18.56	54.03 ± 16.84	5.2%	0.001
PREOP-EGFR	94.11 ± 45.03	95.33 ± 43.71	2.7%	0.087
PS	0.29 ± 0.21	0.29 ± 0.21	1.5%	0.353
GENDER			13.1%	< 0.001
Male	3294 (42.19%)	2795 (35.80%)		
Female	4513 (57.81%)	5012 (64.20%)		
Preop-transfusion with in 30days n(%)			1.6%	0.624
0 units	7275 (93.19%)	7291 (93.39%)		
1 units	295 (3.78%)	273 (3.50%)		
2 or more units	237 (3.04%)	243 (3.11%)		
Intraop-transfusion			1.2%	0.546
0 units	6503 (83.30%)	6531 (83.66%)		
1 units	1304 (16.70%)	1276 (16.34%)		
Postop-transfusion with in 30days			4.2%	0.033
0 units	7494 (95.99%)	7443 (95.34%)		
1 units	202 (2.59%)	257 (3.29%)		
2 units	111 (1.42%)	107 (1.37%)		

Values are n (%) or mean ± SD

Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized diffferences;

PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours

RDW	≤ 15.7%	⬚15.7%	Standardize diff.	P-value
Anesthesia type n(%)			1.2%	0.460
ga	6560 (84.03%)	6526 (83.59%)		
ra	1247 (15.97%)	1281 (16.41%)		
Priority of surgery n(%)			9.9%	< 0.001
Elective	5531 (70.85%)	5872 (75.21%)		
Emergency	2276 (29.15%)	1935 (24.79%)		
Surgical risk			3.9%	0.050
Low	3346 (42.86%)	3379 (43.28%)		
Moderate	3843 (49.23%)	3890 (49.83%)		
High	618 (7.92%)	538 (6.89%)		
RACE			28.3%	< 0.001
Chinese	4953 (63.44%)	5273 (67.54%)		
Indian	757 (9.70%)	785 (10.06%)		
Malay	700 (8.97%)	1045 (13.39%)		
Others	1397 (17.89%)	704 (9.02%)		
ANEMIA			9.0%	< 0.001
None	1862 (23.85%)	1750 (22.42%)		

Values are n (%) or mean ± SD
Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized difffferences;
PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours

RDW	≤ 15.7%	⬚15.7%	Standardize diff.	P-value
Mild	1753 (22.45%)	2053 (26.30%)		
Moderate / Severe	4192 (53.70%)	4004 (51.29%)		
ICUADMGT24H			0.8%	0.619
No	7548 (96.68%)	7559 (96.82%)		
Yes	259 (3.32%)	248 (3.18%)		
RCRI.SCORE			3.9%	0.196
Level 1	3291 (42.15%)	3205 (41.05%)		
Level 2	1501 (19.23%)	1570 (20.11%)		
Level 3	475 (6.08%)	437 (5.60%)		
Level 4	226 (2.89%)	209 (2.68%)		
NA	2314 (29.64%)	2386 (30.56%)		
CVA CATEGORY			4.7%	0.013
NO	5235 (67.06%)	5145 (65.90%)		
Yes	230 (2.95%)	188 (2.41%)		
NA	2342 (30.00%)	2474 (31.69%)		
IHD CATEGORY			5.8%	0.002
NO	4783 (61.27%)	4734 (60.64%)		
Yes	669 (8.57%)	569 (7.29%)		

Values are n (%) or mean ± SD

Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized difffferences;

PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours

RDW	≤ 15.7%	>15.7%	Standardize diff.	P-value
NA	2355 (30.17%)	2504 (32.07%)		
CHF CATEGORY			3.1%	0.160
NO	5405 (69.23%)	5324 (68.20%)		
Yes	193 (2.47%)	175 (2.24%)		
NA	2209 (28.30%)	2308 (29.56%)		
DM CATEGORY			3.1%	0.149
NO	5265 (67.44%)	5150 (65.97%)		
Yes	291 (3.73%)	304 (3.89%)		
NA	2251 (28.83%)	2353 (30.14%)		
ASA CATEGORY			16.5%	< 0.001
level I	1626 (20.83%)	1241 (15.90%)		
level II	3327 (42.62%)	3756 (48.11%)		
level III	2096 (26.85%)	2081 (26.66%)		
level IV-VI	216 (2.77%)	301 (3.86%)		
NA	542 (6.94%)	428 (5.48%)		
Values are n (%) or mean ± SD				
Abbreviations: GA general anesthesia, RA regional anesthesia, SD, Standardized difffferences;				
PREOP-eGFR preoperative estimated glomerular filtration rate (mL/min/1.73m2), PS Propensity score, NA not available, CVA cerebrovascular accidents, IHD ischemic heart disease, CHF congestive heart failure, DM diabetes mellitus requiring insulin therapy; creatinine > 2.0mg/dl, Preop preoperative, Intraop intraoperative, Postop postoperative, RCRI Revised Cardiac Risk Index, ASA American Society of Anesthesiologists, ICU Intensive Care Unit, ICUADMGT24H admission to ICU for > 24 hours				

Association between RDW and 30-day mortality after surgery

In the propensity-score-matched cohort, we examined the association between RDW and 30-day mortality after surgery using a logistic proportional-hazards regression model. In Table 3, the results of the

unadjusted, minimally adjusted, fully adjusted, and propensity score-adjusted analyses are shown simultaneously. In crude model, there was a significant correlation between RDW and 30-day mortality after surgery (OR = 1.877, 95% confidence interval (CI): 1.476–2.388, P<0.00001). Namely, the risk of 30-day mortality after surgery increased by 87.7.0% among high RDW group than non-high RDW group. In the minimally adjusted model (adjusted age, gender, race), the correlation still existed (OR: 2.077, 95%CI: 1.628–2.649, P<0.00001). After adjusting for the full covariates (age, gender, race, eGFR, CVA, DM, IHD, CHF, ASA status, RCRI score, ICUADMGT24H, anemia, priority of surgery, anesthesia type, surgical risk, preoperative blood transfusion with in 30days, intraoperative blood transfusion data, postoperative blood transfusion data), furthermore, we were able to detect a significant statistical connection herewith (OR = 2.146, 95%CI: 1.645–2.799, P<0.00001). In the propensity-score adjusted model, the risk of 30-day mortality after surgery dropped to 86.7% among people with high RDW (OR = 1.867, 95%CI: 1.467–2.376,P<0.00001).

Table 3
The results of multivariate analyses in propensity score matched cohort

Exposure	Non-adjusted(OR,95% CI, P)	Adjust I(OR,95% CI, P)	Adjust II(OR,95% CI, P)	Adjust III(OR,95% CI, P)
THIRTY-DAY MORTALITY				
RDW ≤ 15.7%	Ref	Ref	Ref	Ref
RDW 15.7%	1.877 (1.476, 2.388) < 0.00001	2.077 (1.628, 2.649) < 0.00001	2.146 (1.645, 2.799) < 0.00001	1.867(1.467,2.376) < 0.00001
The results were expressed as odds ratio (95%confidence interval) P-value				
Non-adjusted model adjust for: None				
Adjust I model adjust for: age, gender,race				
Adjust II model adjust for: age, gender,race,perioperative blood transfusion with in 30days, intraoperative blood transfusion,postoperative blood transfusion with in 30days,preoperative eGFR, presence of CVA,DM, IHD, CHF, priority of surgery, anesthesia type, surgical risk, the RCRI score,the ASA status.anemia,ICU .				
Adjust III model adjust for: Propensity score				

Sensitivity analysis

We used inverse probability of treatment weights (IPTW) to generate a weighted cohort. Based on the original cohort and the weighted cohort, we performed the Logistic Proportional-Hazards Regression Model to assess the relationship between RDW and 30-day mortality after surgery. A simultaneous comparison of the unadjusted, minimally adjusted, and fully adjusted models was shown in Table 4. In

both the original and weighted cohorts, the higher RDW was associated with a higher death rate after surgery at 30 days. As compared to non-high RDW group in the full model, the risk of 30-day mortality after surgery in high RDW group increased by 117.0% in the original cohort (OR = 2.277, 95%CI: 1.754–2.683, P < 0.0001) and 122.7% in the weighted cohort (OR = 2.227, 95%CI: 2.009–2.580, P < 0.00001), respectively.

Table 4
Association between RDW and thirty-day mortality in different models of the original and the weighted cohort

	Exposure	Non-adjusted(OR,95% CI, P)	Adjust I(OR,95% CI, P)	Adjust II(OR,95% CI, P)
A	RDW ≤ 15.7%	Ref	Ref	Ref
	RDW15.7%	6.831 (5.738, 8.133) < 0.00001	6.382 (5.345, 7.622) < 0.00001	2.170 (1.754, 2.683) < 0.00001
B	RDW ≤ 15.7%	Ref	Ref	Ref
	RDW15.7%	3.079 (2.760, 3.434) < 0.00001	2.751 (2.465, 3.071) < 0.00001	2.277 (2.009, 2.580) < 0.00001
A In the original cohort; B In the weighted cohort				
Non-adjusted model adjust for: None				
Adjust I model adjust for: age, gender,race				
Adjust II model adjust for: age, gender,race,perioperative blood transfusion with in 30days, intraoperative blood transfusion,postoperative blood transfusion with in 30days,preoperative eGFR, presence of CVA,DM, IHD, CHF, priority of surgery, anesthesia type, surgical risk, the RCRI score,the ASA status.anemia,ICU				

Discussion

This study showed that hig h RDW was significantly associated with higher risks of postoperative 30-day mortality in non-cardiac surgery patients over 18 years of age compared to the non-high group. A number of statistical analyses confirmed this finding, including the doubly robust estimation method, the propensity score-based IPW model, the propensity score-based patient-matching model, the logistic regression based multivariate analysis model and the sensitivity analysis model. According to the study, an uncontrolled high RDW before surgery increased the risk of death rather than critical complications within 30 days of the surgery.

RDW is a well-known independent predictor of mortality and incidence rate in patients undergoing cardiac surgery (30–32). However, in non-cardiac surgery, the impact of RDW on postoperative mortality is still controversial. In a prospective observation of 229 patients undergoing high-risk gastrointestinal surgery, it was confirmed that RDW can predict postoperative mortality(OR RDW-SD = 1.21; P < 0.001, OR RDW-CV =

1.62; P = 0.01 (33). An analysis of non-cardiac surgery patients at the Icelandic National University Hospital was carried out in a retrospective cohort study, in accordance with the preoperative RDW (≤ 13.3%, 13.4–14.0%, 14.1–14.7%, 14.8–15.8%, and > 15.8%), patients were grouped into five predefined groups. All-cause long-term mortality was the primary outcome, with secondary outcomes including 30-day mortality, length of stay, and readmissions within 30 days compared with propensity score matching (PSM) cohort from patients with RDW ≤ 13.3%. Patients with RDW between 14.8% and 15.8%(HR = 1.33; 95%CI, 1.15–1.59; P < 0.001) and above 15.8%(HR = 1.66; 95% CI, 1.4–1.95; P < 0.001) had a higher hazard of mortality, compared with matched controls with RDW ≤ 13.3%. This is basically consistent with our research results. Domestic scholars's study also supports the above conclusion. A propensity matching analysis conducted by Kung-Chuan Cheng et al. (34) on 5315 patients with stage I-II colorectal cancer who underwent inpatient surgery at Chang Gung Memorial Hospital from 2001 to 2018 showed that high RDW remained a negative predictor of overall survival (OS) (HR = 1.49, 95% CI: 1.25–1.78) and disease-free survival (DFS) and cancer-specific survival (CSS) after early colorectal cancer radical surgery. In another study on gastric cancer patients undergoing radical surgery (35), it was found that a high preoperative RDW value was an important predictor of 60 day mortality (17.9 ± 4.3 vs 16.0 ± 3.2; P = 0.015). In patients with RDW ≥ 16%, the disease-free and overall survival rates of advanced gastric cancer decreased (P = 0.04). We found a significant association between RDW and postoperative mortality using the doubly robust estimation method in the propensity-score matched cohort. High RDW increased the risk of 30-day mortality after surgery by 114.6.0%. And the figure dropped to 86.7% after adjusting the propensity score. Thus the results better showed the relationship between RDW and he risk of 30-day mortality after surgery in the real world. Furthermore, we adjusted for different covariates. Several biochemical parameters were adjusted, including eGFR, CVA, DM, IHD, CHF, the RCRI score, ASA status, and hemoglobin. Additionally, our sample size is larger (90,785), and the participants represent four races in Singapore, making it a more representative sample of Asians. The results of our study indicates a correlation between high RDW and a higher risk of 30-day mortality after surgery. Understanding high RDW as a potential risk factor for perioperative period will allow us to communicate risk better with patients and provide more personalized prevention approach and management protocols. The findings of our study are helpful for promoting propensity score methods in correlation studies.

Nevertheless, some people opposed the above view. Xingchen Li et al. (36) retrospectively analyzed 157 patients who underwent radical resection of the liver and found that low preoperative RDW levels were associated with lower survival rates after radical resection of cholangiocarcinoma (ICC), meaning that patients with higher RDW values had better prognosis. Not come singly but in pairs, a retrospective study involving 380 patients with colorectal cancer liver metastasis (CRLM) who underwent liver resection revealed a significant correlation between preoperative, red blood cell distribution width- coefficient of variation(RDW-CV) elevation and better postoperative progression free survival (PFS) through univariate and multivariate Cox regression analysis (mPFS: 5.0 vs. 8.9 months, P = 0.007; mOS: 59.0 vs. 42.0 months, P = 0.041) (37). Pedrazzani C et al. (15) analyzed 591 patients who underwent colorectal cancer surgery and found that patients with a value higher than 14.1% (H-RDW) did not show a shorter cancer-related survival period. Meanwhile, according to Tumor Node Metastasis(TNM) staging, H-RDW is only

associated with a decrease in postoperative survival rate in stage (p = 0.001), but H-RDW does not seem to affect survival rates in stages II-IV.

Inconsistent findings may be caused by the following factors: (1) Study participants are diverse in terms of their racial, gender, nationality, age, and other characteristics. (2) The sample size of different studies varies greatly. (3) There were various confounding variables taken into account in these studies to adjust for the relationship between RDW and postoperative mortality. (4) Results vary greatly depending on the time between follow-ups.(5)There are different ways to handle confounding factors. As a result of our findings, the existing literature supports the hypothesis that high RDW increases 30-day mortality after surgery, highlighting the importance of reducing RDW before surgery.

There is still some uncertainty regarding whether high RDW is directly related to postoperative mortality. The increase of RDW reflects the changes of erythrocyte homeostasis, including erythropoiesis disorder, abnormal erythrocyte metabolism and survival, which may be caused by various abnormal conditions in the body, including inflammation, oxidative stress, malnutrition, erythrocyte fragmentation, hypertension, dyslipidemia and erythropoietin abnormality (38–41). Patients with high RDW often have more significant inflammatory reactions and malnutrition before surgery, inhibiting the proliferation of bone marrow primitive cells, allowing immature red blood cells to enter the bloodstream. At the same time, aging red blood cells in the bloodstream are reduced, resulting in smaller or larger red blood cells present in the bloodstream, ultimately leading to an increase in RDW (42). Perlstein et al. (43)found that the increase in RDW is closely related to certain inflammatory response markers such as CRP, erythrocyte sedimentation rate, IL-6, etc. RDW may be a comprehensive response of a series of inflammatory factors acting on the body during sepsis, that is, the oxidative stress response caused by the action of inflammatory factors on the body. Inflammation leads to changes in the nervous and endocrine systems in the body, activates the related renin angiotensin aldosterone system, promotes the production of erythropoietin (EPO), and stimulates red blood cell proliferation (44);Inflammation, in turn, affects bone marrow hematopoietic function and iron metabolism (45). A series of inflammatory factors inhibit the maturation of red blood cells, leading to obstacles and ineffective generation of mature red blood cells, increased heterogeneity of red blood cells, and an increase in RDW (46).Therefore, RDW can reflect the general health status, subclinical and clinical disease status, and provide valuable information for predicting the prognosis of patients with various common acute and chronic diseases, such as diabetes (47), traumatic brain injury (TBI) (48); and oxidative stress (49) association.

Study strengths and limitations

Strengths of this study include the following. As far as we know, patients undergoing noncardiac surgery have fewer cohort studies using propensity score matching to explore the relationship between preoperative RDW and postoperative 30-day mortality. First, a cross-sectional study was conducted to investigate the relationship between RDW and postoperative prognosis using the PSM. Observational studies have increasingly used PSM methods in recent years. With the PSM method, a wide range of data requirements can be satisfied, including reducing inter-group differences, balancing confounding

variables, and achieving the effect of "similar randomization". Second, to reduce treatment selection bias inherent in retrospective studies, in order to minimize baseline differences between groups, we employ the doubly robust estimation method. Third, using a sensitivity analysis, we validated the data's reliability. As part of this study, IPTW was primarily used to establish a weighted cohort and further investigate the relationship between RDW and postoperative 30-day mortality rate. Fourth, unlike previous retrospective cohort studies, this study included a larger sample size of participants. Additionally, this clinical database contained detailed information about demographics, preexisting comorbidities, and risk assessment methods that can affect morbidity and mortality independently.

However, there are several limitations to the present stud. First, the study population consisted of only Asian patients. In order to enhance the reliability of the data, multicenter research can be conducted to expand the study population. And the raw data did not provide information on surgical intervention during patient follow-up. This limits the exploration of this study, in the future, we can consider designing our studies or collaborating with other researchers to collect as many variables as possible, including information on surgical intervention during patient follow-up, the investigators must have homogenous groups. Second, in this study, published data were analyzed secondary, it was not possible to eliminate residual and/or unmeasured confounding factors from the evaluated associations(e.g. inflammatory markers and socioeconomic factors) and investigate the long-term relationship between RDW and health outcomes. Third, although the PSM tried to balance known confounding variables to the best of its ability, it did not ensure that all measures of baseline characteristics matched, nor did it account for the influence of unknown variables. As a measure of reducing interference from variables, we set the calliper width to 0.01. Fourth, in addition, other diseases, as well as fat and carbohydrate metabolism, can also affect RDW (50, 51). Therefore, RDW should be evaluated in combination with other morphological and clinical parameters. Fifth, it discharged patients with high-risk injuries, such as nerve injuries, burns, and serious infections, despite the fact that it was originally aimed at non-cardiac surgery populations. Sixth, our research objective is to explore the impact of baseline RDW on mortality occurring within 90 days, the time span in the raw data is indeed very large. This might lead to selection bias.

Conclusion

According to the results of this observational, propensity score-matched cohort study, there is a significant correlation between higher RDW and higher 30-day mortality, that is to say, patients over the age of 18 with high preoperative RDW who undergo non-cardiac surgery have a worse postoperative prognosis than those with normal RDW.

Abbreviations

RDW, red blood cell width; H-RDW, high RDW; PS, Propensity score; CI, Confidence Interval; OR, Odds; NA, not available; CVA, cerebrovascular accidents; eGFR, estimated Glomerular Filtration Rate; IHD, ischemic heart disease; CHF, congestive heart failure; DM, diabetes mellitus; Preop, preoperative; Intraop, intraoperative; Postop, postoperative; RCRI, Revised Cardiac Risk Index; ASA, American Society of

Anesthesiologists; ICU, Intensive Care Unit; ICUADMGT24H, admission to ICU for >24 hours; GA, general anesthesia; RA, regional anesthesia; SD, Standard deviation.

Declarations

Authors' contributions

Wei Wei conceived the research, drafted the manuscript, Bishan Feng did the statistical analysis. Haofei Hu revised the manuscript and designed the study. Zimiao Chen and Xiaojie Liu took part in the discussion. All authors read and approved the final manuscript.

Acknowledgments

Availability of data and materials

Data can be downloaded from the 'DATADRYAD' database (www.Datadryad.org).

Consent for publication

Not applicable.

Conflict of interest

The authors declare that they have no competing interests.

Ethical approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all Participants. This study has been approved by the SingHealth Centralised Institutional Review Board (CIRB). (Singhealth CIRB 2014/651/D).

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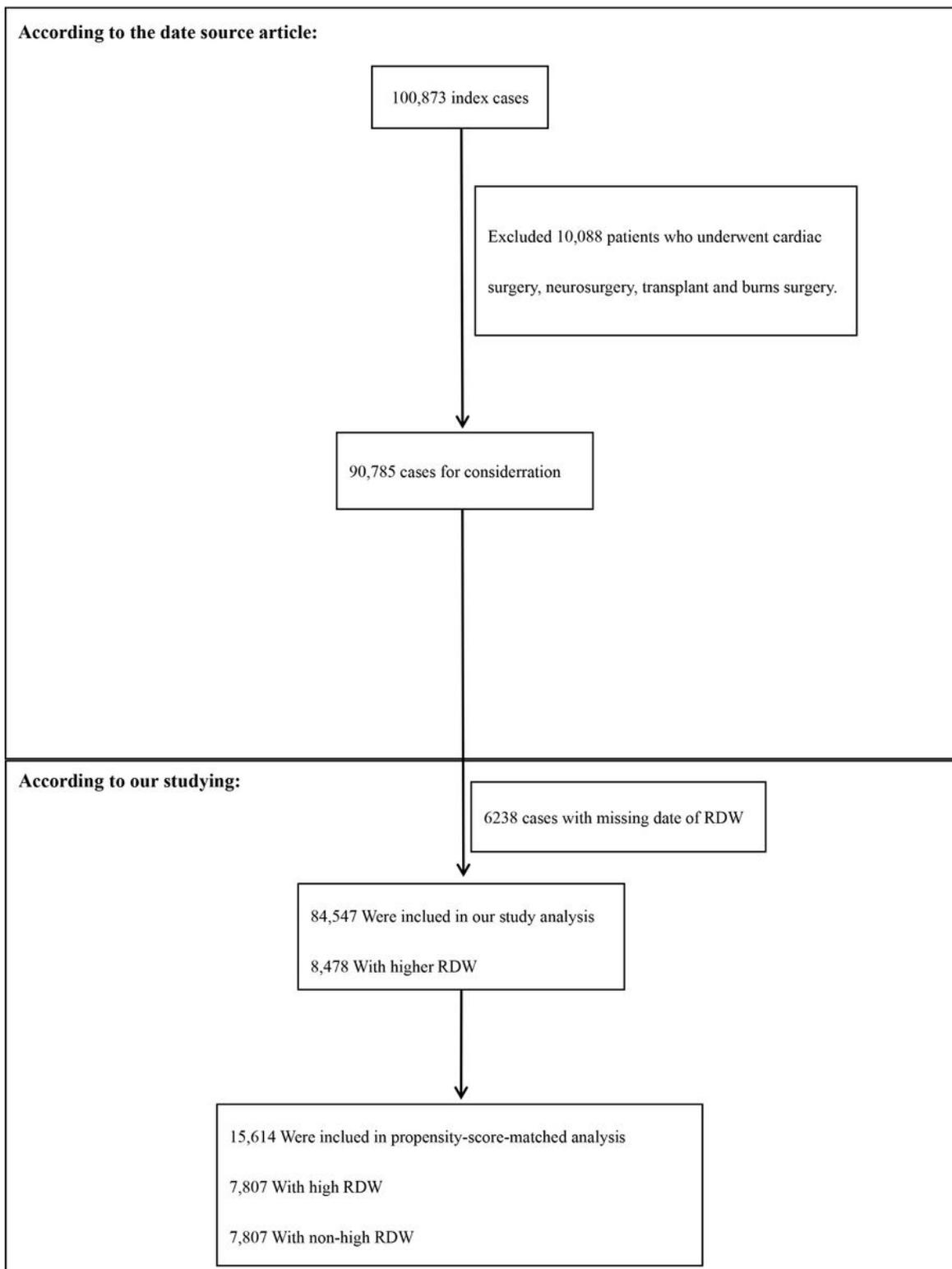
Figures

According to the date source article:

100,873 index cases

Excluded 10,088 patients who underwent cardiac surgery, neurosurgery, transplant and burns surgery.

90,785 cases for considerration

According to our studying:

6238 cases with missing date of RDW

84,547 Were included in our study analysis

8,478 With higher RDW

15,614 Were inclued in propensity-score-matched analysis

7,807 With high RDW

7,807 With non-high RDW

Figure 1

Study Population.

Figure 1 showed the inclusion of participants. 100,873 participants were assessed for eligibility in the original study. We excluded patients who underwent cardiac surgery, neurosurgery, transplant and burns surgery, and with missing date of RDW. The final analysis included 84547 subjects in the present study.