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Original Research Article

ORIGINAL RESEARCH ARTICLE

The association between elevated preoperative red cell distribution width and worsening kidney function after noncardiac operation. A propensity score and competing risk weighted retrospective cohort study

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Background: Elevated red cell distribution width (RDW) is associated with increased postoperative mortality, but less is known about kidney outcomes. This study investigated the association between elevated preoperative RDW and postoperative worsening of long-term kidney function and incidence of acute kidney injury.
Methods: This retrospective cohort study included patients ≥18 yr undergoing noncardiac operation at Landspitali—The National University Hospital of Iceland between 2005 and 2018. Outcomes were compared between groups with elevated preoperative RDW (13.3–14.0%, 14.0–14.7%, 14.7–15.8%) and a propensity score-matched cohort (RDW ≤13.3%) using Fine–Gray competing risk regression analysis, with death as a competing event. The primary outcome was time to worsening of at least one estimated glomerular filtration rate (eGFR) category sustained for 3 months. Secondary outcomes were acute kidney injury, length of hospital stay, and 30-day readmission rate.
Results: Out of 63 056 operations included in this study, 55 724 were available for propensity score-matched analysis. The hazard of long-term eGFR worsening was higher for patients with RDW between 14.0% and 14.7%: hazard ratio (HR) 1.23 (95% confidence interval [CI] 1.13–1.35), 14.7% and 15.8%: HR 1.20 (95% CI 1.07–1.34), and >15.8%: HR 1.16 (95% CI 1.00–1.34) compared with matched controls (RDW <13.3%), adjusted for death as a competing event. For secondary outcomes there was no difference in acute kidney injury, but increased risk of readmission for patients with RDW of 14.0–14.7% (9.8% *vs* 8.5%, *P*=0.01), 14.7–15.8% (12.2% *vs* 10.1%, *P*=0.001), and >15.8% (14.9% *vs* 11.4%, *P*<0.001).
Conclusions: Elevated preoperative RDW was associated with long-term worsening of eGFR category after operation.

Keywords: chronic inflammation; chronic kidney disease; noncardiac operation; preoperative; red cell distribution width; renal outcomes; worsening kidney function

Chronic kidney disease (CKD) affects 9% of the population.[1] At onset, nephron damage mediated by ischaemia, inflammation, or structural abnormalities leads to compensatory hypertrophy of the remaining nephrons. Subsequent glomerular degeneration and fibrosis causes irreversible reduction in the filtration capacity of the kidneys and drives further progression of CKD.[2]

Acute kidney injury (AKI) is an important cause of both onset and progression of CKD.[3,4] AKI is a common complication after major operations because of direct affection on kidney microcirculation, oxygen demand, and inflammation.[5,6] Furthermore, changes in oxygen delivery of blood to the kidneys during the perioperative period has been

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suggested as a potential cause, supported by the increased risk of postoperative AKI for patients with anaemia.[7]

Red cell distribution width (RDW) measures the variability in the size of circulating red blood cells and is routinely assessed before surgery. Elevated RDW has been associated with worse survival in several clinical cohorts, including patients with kidney disease,[8] malignancy,[9] after noncardiac operations,[10] and in intensive care.[11] The mechanism underlying this is unknown but has been suggested to be secondary to association of RDW with long-term inflammation.[10] Inflammation inhibits red blood cell maturation, and as compensation red blood cell lifetime is extended, delaying red blood cell clearance to maintain red blood cell mass and oxygen delivery.[12] This mechanism will increase RDW.[10,12,13]

Elevated RDW after cardiac operations in patients with AKI has been associated with both severity of AKI and mortality.[14] Elevated RDW has also been independently associated with faster eGFR decline in non-operative individuals with CKD.[15] This could possibly be a result of RDW serving as a surrogate marker of chronic inflammation or reflecting alterations in microcirculation. Additionally, it is possible that recovery from postoperative AKI is slower with elevated RDW.

The aim of this study was to examine the association of elevated RDW before operation and postoperative short- and long-term kidney outcomes. We hypothesised that there was an association between elevated preoperative RDW and postoperative worsening of long-term kidney function and also an increased risk of postoperative AKI.

Methods

Study cohort and data collection

This was a retrospective single-centre cohort study of patients aged ≥18 yr who underwent a noncardiac operation at Landspitali University Hospital in Iceland between December 2005 and December 2018 and had an RDW measurement within 30 days before surgery.

This study was approved by the Icelandic Bioethics Committee, Reykjavík, Iceland (VSN-14-139), and the Research Ethics Committee at Landspítali University Hospital, 16 October 2014 with later addendums. Individual consent was waived because of the retrospective design of the study.

Details of the data collection and modification has been described elsewhere.[10,16] In short, procedural information was categorised by the NOMESCO (Nordic Medico-Statistical Committee) operational classification and comorbidities were classified using registered primary care and hospital diagnoses classified via International Classification of Diseases, Ninth or Tenth Revision (ICD-9/10). Patient characteristics, mode of operation, and anaesthesia were obtained from electronic health records. Medication prescriptions filled up to a year before surgery were obtained from the national prescription database. Laboratory values before, during, and after operation were collected from a nationwide laboratory database, including complete blood counts and serum creatinine measurements.

Patients were separated into five groups by preoperative RDW values (≤13.3%, 13.3–14.0%, 14.0–14.7%, 14.7–15.8%, and >15.8%), as in previous studies.[10,11] The primary and secondary outcomes were analysed by comparing every group of the four elevated RDW groups (>13.3%) with propensity score-matched (PSM) control patients from the normal RDW (≤13.3%) group, followed by competing risk analysis for each paired cohort.

Covariates and outcomes

The five RDW groups were described with baseline patient characteristics, major comorbidities, acuity of operation, and preoperative medications. For each serum creatinine measurement, the estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI$_{2009}$ equation.[17,18] Kidney function was then classified into five eGFR categories (Category 1: ≥90 ml/min/1.73 m^2, Category 2: 60-89 ml/min/1.73 m^2, Category 3a: 45-59 ml/min/1.73 m^2, Category 3b: 30-44 ml/min/1.73 m^2, Category 4: 15-29 ml/min/1.73 m^2, using the highest category sustained for three months or more. This classification mimics the eGFR part of the CKD classification by the Kidney Disease: Improving Global Outcomes (KDIGO).[18] Category 5: < 15 ml/min/1.73 m^2, representing end-stage CKD was excluded from this study as further eGFR category worsening is not possible.

The predefined primary outcome was time to worsening of eGFR category defined as increment of at least one eGFR category sustained for a minimum of 3 months. Follow-up for eGFR worsening was up to 5 yr.

The secondary outcomes were AKI within 30 days after operation, length of primary hospital stay (LOS), and 30-day readmission rate. AKI was defined using the serum creatinine part of the KDIGO definition as elevation of creatinine by a minimum of 26.5 μmol L^{-1} within 2 days or at least 1.5 times the patients preoperative baseline creatinine within 7 days after surgery.[19]

Statistical analysis

Categorical data were expressed as numbers with percentage and group difference was compared with the $\chi 2$ test. Continuous data were expressed as mean with standard deviation (SD) and group differences were compared with t-test or analysis of variance (ANOVA). A PSM control cohort was created for each of the four elevated RDW groups using control individuals from the RDW ≤13.3% group. The Matchit package in R (R Foundation for Statistical Computing, Vienna, Austria) was used for pairing with the nearest neighbour method. To constrain the difference between pairs the calliper was set at 0.1.[20] Individuals with missing data in the PSM analysis were excluded from the comparison with PSM controls.

Matching variables, based on our previous studies,[10,16] included sex, age, year of operation, preoperative haemoglobin value (obtained up to 30 days before operation), hypertension, diabetes mellitus, ischaemic heart disease, congestive heart failure, chronic obstructive pulmonary disease, liver disease, benign neoplasm, and malignant neoplasm. Additionally, we matched based on frailty risk class predicting 30-day mortality or readmission and hospital LOS,[21] and American Society of Anesthesiologists (ASA) physical status classification. Matching for preoperative filling of prescriptions was done for angiotensin converting enzyme (ACE) and angiotensin receptor blocker (ARB) inhibitors, beta blockers, statins, diuretics, NSAID, and corticosteroids. Additionally, patients were matched for anatomical location, extent, acuity and duration of operation, and primary mode of anaesthesia. Importantly, patients were also matched for eGFR category before operation. Patients not paired after PSM or without available data on progression of kidney function were excluded from further analysis.

The difference in worsening of eGFR category between each of the matched cohorts was depicted graphically using

Kaplan–Meier curves using the survival package in R (R Foundation for Statistical Computing). Hazard ratios (HR) with 95% confidence intervals (CI) were quantified using the Cox proportional hazard model for each paired cohort. The proportionality assumption was tested using cox.zph. The primary outcome, worsening of eGFR category, was then analysed with death as a competing outcome defined as time-to-event, and HR calculated for each comparison with Fine–Gray modelling. The relationship between competing variables, death, and worsening of eGFR category, was then depicted in cumulative incidence curves using the survival package in R (R Foundation for Statistical Computing).

As previously described,[16] original data handling and building of the database was carried out by one the study's authors (MIS) via custom-made JAVA scripts. All analyses were performed using R version 3.5.1 (R foundation for Statistical Computing), and using RStudio version 1.4.1106 (Rstudio, Inc, Boston, MA, USA). In addition, Tidyverse, Survival, Epitools, Survminer and TableOne packages in R (R foundation for Statistical Computing) were used for statistical analysis.

Results

Cohort characteristics

After exclusion of 20 953 patients without available preoperative RDW, the dataset included 63 056 operations performed on 43 105 patients (Fig 1). After exclusion of operations with missing data, 55 724 were used for analysis, with mean follow-up time of 5.64 yr (0.0–13.41 yr).

With increasing RDW, patients were older, had higher frailty risk, higher ASA physical status scores and higher rates of individual comorbidities (Table 1). The rates of diabetes mellitus, chronic obstructive pulmonary disease, ischaemic heart disease, and chronic heart failure increased with elevation of RDW. Patients with higher RDW were more likely to have advanced eGFR category with 3.4% of patients in the RDW >15.8% group having eGFR category 4, compared with 1.0% of patients in the RDW ≤13.3% group. Most commonly performed procedures were orthopaedic (29.7%) and abdominal (24.5%). Gynaecological operation were more common in RDW ≤13.3% and abdominal in RDW >15.8% (Table 1).

The mean preoperative haemoglobin and mean corpuscle volume (MCV) levels were lower while platelets and C-reactive protein (CRP) were higher in groups with elevated RDW (Table 1).

Unadjusted outcomes

The unadjusted hazard ratio for long-term worsening of eGFR category after noncardiac operation was 2.1 (95% CI 1.9–2.1), 2.8 (95% CI 2.6–3.0), 3.4 (95% CI 3.1–3.7), and 3.6 (95% CI 3.3–4.0) in groups with RDW 13.3–14.0%, 14.0–14.7%, 14.7–15.8%, and >15.8%, respectively, compared with the reference group with RDW ≤13.3%. Similarly, the incidence of AKI after operation was 7.4%, 9.5%, 10.3%, and 10.9% in groups with RDW 13.3–14.0%, 14.0–14.7%, 14.7–15.8%, and >15.8%, respectively, compared with 5.7% in the reference group with RDW ≤13.3% group (Table 2). Both readmission rate and hospital LOS in days increased with elevated RDW (Table 2).

Propensity score-matched analysis

After matching, PSM controls from the RDW ≤13.3% reference group were available for 13 395 (95.7%), 7838 (92.7%), 4729 (84.8%), and 3097 (69.1%) patients from RDW groups 13.3–14.0%, 14.0–14.7%, 14.7–15.8%, and >15.8%, respectively. After further exclusion of individuals without information for worsening of eGFR category, 4521 (34%), 2814 (36%), 1805 (38%), and 1124 (36%) of control patients were available for further analysis and 4699 (35%), 3030 (39%), 1842 (39%), and 1079 (35%) in the RDW groups 13.4–14.0%, 14.0–14.7%, 14.7–15.8%, and >15.8%, respectively (Fig 1). The dropout for missing eGFR progress was randomly distributed between groups of varying RDW and cases and controls.

There was no difference in worsening of eGFR category for the RDW group 13.3–14.0%, HR 0.89 (95% CI 0.7–1.0) and in the highest RDW group >15.8%, HR 1.17 (95% CI 0.8–1.6) (Fig 2) compared with their PSM controls. However, higher hazard was observed for worsening of eGFR category in patients in the RDW group 14.0–14.7%, HR 1.24 (95% CI 1.0–1.5) and 14.7–15.8% with HR 1.44 (95% CI 1.1–1.9), compared with their PSM controls.

For secondary outcomes there was significantly increased risk of readmission for patients with RDW of 14.0–14.7% (9.8% *vs* 8.5%, P=0.01), 14.7–15.8% (12.2% *vs* 10.1%, P=0.001), and >15.8% (14.9% *vs* 11.4%, P<0.001) compared with PSM controls (Table 3). LOS was also significantly increased in patients with RDW 14.0–14.7% compared with PSM controls. The frequency of AKI was similar between any of the groups and PSM controls (Table 3).

Competing risk analysis

For further analysis of the PSM results we evaluated a model with two competing events: death from any cause and worsening of eGFR category.

With Fine–Gray competing risk regression analysis there was no difference in worsening of eGFR category for the RDW group 13.3–14.0%, HR 1.04 (95% CI 0.97–1.12; Fig 3a) compared with their PSM controls. However, a higher hazard was observed for worsening of eGFR category in patients in the RDW groups 14–14.7%, HR 1.23 (95% CI 1.13–1.35; Fig 3b) and 14.7–15.8%, HR 1.2 (95% CI 1.07–1.34; Fig 3c) compared with their PSM controls. Furthermore, in contrast with PSM results without competing risk adjustment, a higher hazard for worsening of eGFR category was observed in RDW group >15.8%, HR 1.16 (95% CI 1.00–1.34; Fig 3d) compared with their PSM controls.

There was not a significant difference in long-term survival for patients in any of the RDW groups 13.3–14.0%, HR 1.09 (95% CI 0.92–1.31; Fig 3a), 14–14.7%, HR 1.01 (95% CI 0.82–1.25; Fig 3b) or 14.7–15.8%, HR 1.1 (95% CI 0.86–1.41; Fig 3c) and >15.8%, HR 1.23 (95% CI 0.93–1.63; Fig 3d) compared with their PSM controls.

Discussion

The primary finding was an association between elevated preoperative RDW and eGFR category worsening after noncardiac operation after meticulous propensity score matching and accounting for death as a competing outcome. While the effect size was overall small limiting the direct clinical applications for an individual receiving perioperative care, our results allow for further understanding and speculations on how the distribution of red cell size mediates its negative outcomes via end-organ effects. Additionally, while overall effect is small, our results raise the question if there is a specific combination of patient and procedure characteristics

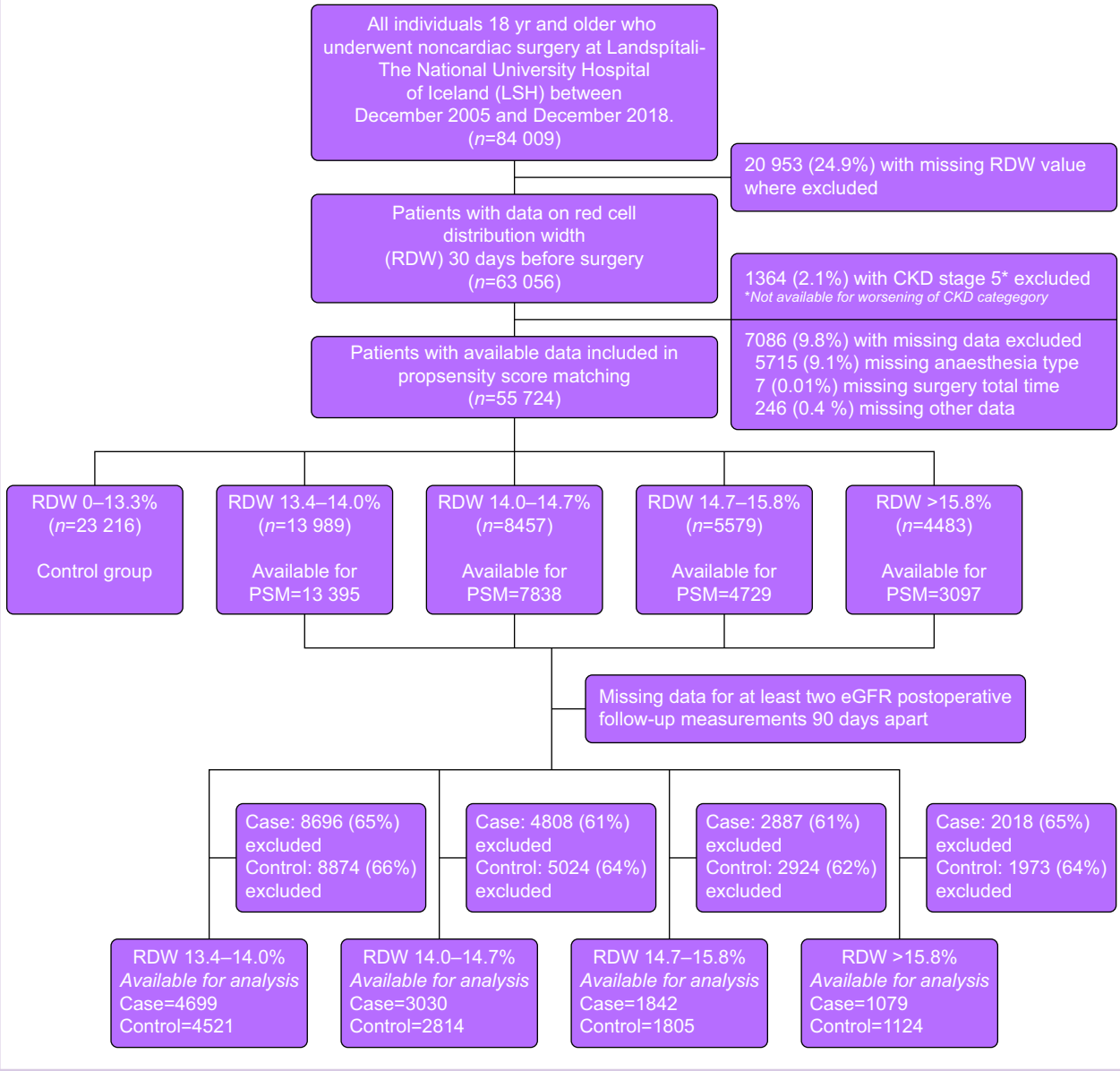

Fig 1. *A flowchart showing inclusion and exclusion steps, and the generation of five red cell distribution width (RDW) groups, with RDW ≤13.3%, 13.3–14.0%, 14.0–14.7%, 14.7–15.8%, and >15.8.* CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; PSM, propensity score matching.

where an elevated RDW indicates limited kidney reserve, and adjustments should be made to the perioperative care to mediate the risk of impaired kidney function. Thus, elevated RDW before operation may indicate susceptibility to long-term worsening of eGFR category, and possibly progression of CKD. This could be caused by the effects of chronic illness,[10] driven by chronic inflammation affecting both CKD progression and RDW or the effects of altered red blood cell size on microcirculation of the kidneys.

Previous studies have focused on elevated RDW association with AKI after cardiac operations.[14,22] Meta-analysis of five studies involving 21 129 patients by Frentiu and colleagues[22] indicated that elevated preoperative RDW increased the risk of AKI after cardiac operations (pooled odds ratio 1.30 [95% CI 1.19–1.41]). While unadjusted analysis indicated increase in the risk of AKI with higher RDW, this was not observed in the matched analysis, possibly because of higher frequency of unmatched individuals in the high RDW groups. Another contributor might be the dependence of AKI onset on baseline kidney function, which is among matched variables in the statistical analysis. The variability in frequency of AKI between different procedural groups might also be a contributing factor.

While our cohort is vastly different, a relationship between long-term progression of CKD and elevated RDW after kidney transplantation has been described by Ujszaszi and

Table 1 Patient characteristics for groups of increasing RDW. Data are presented as *n* (%) for count data and mean [(standard deviation)] for continuous data. ACE, angiotensin converting enzyme; ARBs, angiotensin-II receptor blockers; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; MCV, mean corpuscle volume; RDW, red cell distribution width; SD, standard deviation.

RDW value	(Referent) ≤13.3%	13.3–14%	14–14.7%	14.7–15.8%	>15.8%	*P*-value
n	23 308	14 067	8486	5607	4502	
Age (yr), mean (range)	53.2 (18–100)	60.7 (18–102)	64.5 (18–104)	65.1 (18–107)	64.1 (18–103)	<0.001
Female sex	13 050 (56.0)	7883 (56.0)	4830 (56.9)	3186 (56.8)	2579 (57.3)	0.288
Comorbidities						
Diabetes mellitus	784 (3.4)	696 (4.9)	514 (6.1)	490 (8.7)	446 (9.9)	<0.001
Hypertension	6927 (29.7)	5938 (42.2)	4013 (47.3)	2753 (49.1)	2128 (47.3)	<0.001
COPD	526 (2.3)	561 (4.0)	533 (6.3)	434 (7.7)	466 (10.4)	<0.001
Ischaemic heart disease	3105 (13.3)	2788 (19.8)	2097 (24.7)	1557 (27.8)	1294 (28.7)	<0.001
Congestive heart failure	773 (3.3)	861 (6.1)	824 (9.7)	796 (14.2)	814 (18.1)	<0.001
Malignant neoplasm	4412 (18.9)	3374 (24.0)	2307 (27.2)	1732 (30.9)	1845 (41.0)	<0.001
eGFR category						<0.001
1	9924 (42.6)	4388 (31.2)	2237 (26.4)	1434 (25.6)	1187 (26.4)	
2	9829 (42.2)	6614 (47.0)	4045 (47.7)	2597 (46.3)	2049 (45.5)	
3a	2402 (10.3)	1955 (13.9)	1332 (15.7)	835 (14.9)	693 (15.4)	
3b	910 (3.9)	877 (6.2)	657 (7.7)	550 (9.8)	410 (9.1)	
4	243 (1.0)	233 (1.7)	215 (2.5)	191 (3.4)	163 (3.6)	
Frailty score class						<0.001
Low	19 220 (82.5)	10 610 (75.4)	5785 (68.2)	3394 (60.5)	2436 (54.1)	
Intermediate	3756 (16.1)	3087 (21.9)	2361 (27.8)	1851 (33.0)	1669 (37.1)	
High	332 (1.4)	370 (2.6)	340 (4.0)	362 (6.5)	397 (8.8)	
ASA physical status						<0.001
1	7172 (30.8)	2477 (17.6)	889 (10.5)	456 (8.1)	362 (8.0)	
2	11 932 (51.2)	7757 (55.1)	4398 (51.8)	2508 (44.7)	1668 (37.1)	
3	3683 (15.8)	3310 (23.5)	2694 (31.7)	2095 (37.4)	1914 (42.5)	
4	452 (1.9)	459 (3.3)	451 (5.3)	476 (8.5)	498 (11.1)	
5	69 (0.3)	64 (0.5)	54 (0.6)	72 (1.3)	60 (1.3)	
Type of operation						
Orthopaedic	6251 (26.8)	3913 (27.8)	2437 (28.7)	1556 (27.8)	1012 (22.5)	<0.001
Vascular	2014 (8.6)	1202 (8.5)	721 (8.5)	497 (8.9)	402 (8.9)	0.875
Abdominal	5109 (21.9)	2875 (20.4)	1804 (21.3)	1364 (24.3)	1371 (30.5)	<0.001
Neurologic	2135 (9.2)	1195 (8.5)	621 (7.3)	335 (6.0)	219 (4.9)	<0.001
Urologic	2083 (8.9)	1542 (11.0)	936 (11.0)	532 (9.5)	452 (10.0)	<0.001
Thoracic	256 (1.1)	239 (1.7)	179 (2.1)	139 (2.5)	104 (2.3)	<0.001
Gynaecologic	2871 (12.3)	1515 (10.8)	798 (9.4)	521 (9.3)	484 (10.8)	<0.001
Endocrinologic	687 (2.9)	343 (2.4)	172 (2.0)	98 (1.7)	54 (1.2)	<0.001
Blood results (preoperative)						
Haemoglobin (g L^{-1})	136 (16)	134 (17)	130 (19)	123 (19)	114 (18)	<0.001
Platelets $\times 10^9 L^{-1}$	242 (72)	239 (75)	243 (86)	260 (105)	274 (121)	<0.001
MCV	51 (42)	45 (42)	43 (42)	41 (41)	42 (39)	<0.001
CRP	24 (47)	30 (60)	39 (73)	50 (80)	63 (90)	<0.001
White blood cells $\times 10^9 L^{-1}$	8.7 (3.8)	8.6 (3.8)	8.9 (4.1)	9.4 (5.4)	9.7 (8.7)	<0.001
Medication filled in the year preceding operation						
Anticoagulant	2303 (9.9)	2373 (16.9)	1912 (22.5)	1577 (28.1)	1474 (32.7)	<0.001
Antiplatelet	1638 (7.0)	1512 (10.7)	1131 (13.3)	893 (15.9)	813 (18.1)	<0.001
ACE inhibitor	2105 (9.0)	1758 (12.5)	1245 (14.7)	851 (15.2)	661 (14.7)	<0.001
ARBs	3224 (13.8)	2795 (19.9)	1926 (22.7)	1193 (21.3)	901 (20.0)	<0.001
Beta blocker	5028 (21.6)	4102 (29.2)	2855 (33.6)	2025 (36.1)	1750 (38.9)	<0.001
Statin	4223 (18.1)	3672 (26.1)	2593 (30.6)	1769 (31.5)	1338 (29.7)	<0.001
Diuretics	3518 (15.1)	2968 (21.1)	2220 (26.2)	1635 (29.2)	1471 (32.7)	<0.001
Respiratory	6073 (26.1)	4169 (29.6)	2758 (32.5)	1970 (35.1)	1606 (35.7)	<0.001

colleagues.[23] In this study of 723 kidney transplant patients, RDW >14% increased the risk of worse kidney function after 365 days compared with the reference group with RDW <14%. This is consistent with our results, despite methodological differences. Our study implemented preoperative RDW and propensity score matching, different from Ujszaszi and colleagues study that used a more homogenous cohort.[23]

While most of our patients fall within the reference range for RDW in our laboratory (between 12.5% and 16.7%), reference ranges have been reported to vary based on age and both ethnicity and gender.[24] We therefore chose to categorise RDW based on classes described in earlier publications describing associations between RDW and adverse clinical outcomes. This likely reflects that reference ranges are population-based, not disease-focused.[25]

Our study found increased hazard for eGFR category worsening in RDW 14–14.7% and 14.7–15.8% and the highest RDW >15.8% group, although the effect was smaller. The difference between groups in worsening of eGFR category may lie in the elevated cumulative incidence of mortality over longer

Table 2 Unadjusted postoperative outcomes based on preoperative RDW. AKI, acute kidney injury; IQR, interquartile range; LOS, length of hospital stay; RDW, red cell distribution width.

RDW	(Referent) ≤13.3%	13.3–14%	14–14.7%	14.7–15.8%	>15.8%	P-value
n	23 308	14 067	8486	5607	4502	
AKI	211 (5.7)	239 (7.4)	217 (9.5)	182 (10.3)	166 (10.9)	<0.001
Thirty-day readmission	1757 (7.5)	1151 (8.2)	868 (10.2)	730 (13.0)	762 (16.9)	<0.001
LOS (median [IQR])	2 [1–4]	2 [1–5]	3 [1–6]	3 [1–8]	4 [1–10]	<0.001

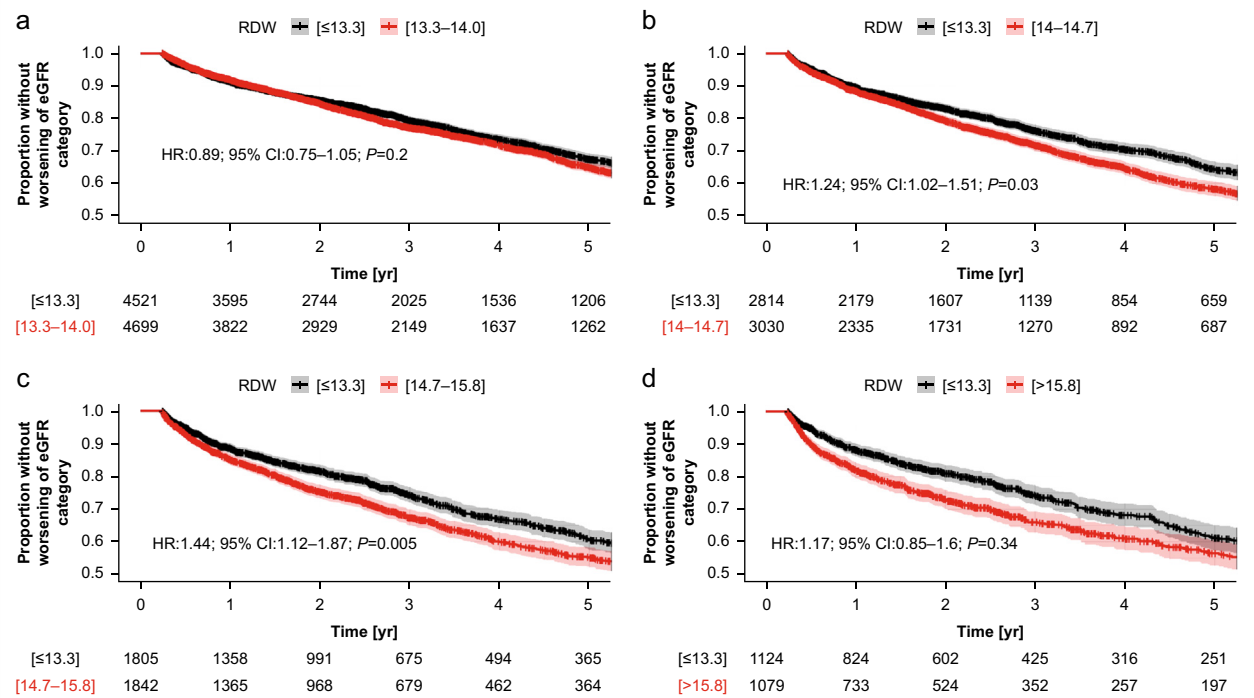

Fig 2. Worsening of eGFR category for (a) RDW 13.3–14%, (b) RDW 14–14.7%, (c) RDW 14.7–15.8%, and (d) RDW >15.8% groups compared with propensity score-matched controls with RDW <13.3%. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RDW, red cell distribution width.

follow-up time for the RDW >15.8% group, reducing opportunities for worsening of eGFR category as previously described by Liu and colleagues.[26] Our previous subset study of the current study patients showed highest hazard for mortality after operation in the RDW >15.8% group,[10] that supports this theory.

A possible explanation of the relationship between CKD progression and elevated RDW is the presence of chronic inflammation before operation associated with both progression of CKD and elevated RDW. In a review by Stenvinkel and colleagues,[27] chronic inflammation and metabolic pathways were suggested to be the major driver for the progression of CKD via tubulointerstitial fibrosis, vascular calcification, and mesangial expansion.[27]

Given that chronic inflammation is associated with CKD progression, the association with elevated RDW could be explained by the blood tissue response to chronic inflammation.[10] During long-term inflammation, cytokines inhibit production of blood cells in the bone marrow causing anaemia.[28] To compensate for decreased production, the blood tissue extends the lifespan of existing red blood cells, causing a shift in the red blood cells size-dependent clearance threshold.[12] This alteration retains smaller and larger blood cells that are otherwise removed from circulation, causing increased variability in MCV and elevated RDW.[12] Vascular calcification in kidneys driven by inflammation and variation in size of blood cells might also lead to further atherosclerosis and thrombosis in the kidneys, amplifying CKD progression.[27,29]

A follow-up study could explore if normalised RDW before operation would improve postoperative outcomes. Longitudinal measurements of RDW have been suggested to be more accurate prognosticators than admission values in patients with heart failure, although impact of normalised RDW has not been addressed.[30] A study of patients with coronary

Table 3 Postoperative secondary outcomes compared with propensity score-matched controls. AKI, acute kidney injury; IQR, interquartile range; LOS, length of hospital stay; NA, not applicable; RDW, red cell distribution width.

	Control (%) ≤13.3%	Case (%) 13.3–14%	P-value	Control (%) ≤13.3%	Case (%) 14–14.7%	P-value
AKI	882 (6.6)	955 (7.1)	0.58	588 (7.5)	640 (8.2)	0.42
Thirty-day readmission	1094 (8.2)	1076 (8.0)	0.7	666 (8.5)	767 (9.8)	0.01
LOS (median [IQR])	4.5 [1–5]	4.8 [1–5]	0.18	5.3 [1–6]	6.2 [1–6]	0.04
n TOTAL	13 395	13 395	NA	7838	7838	NA
	Control (%) ≤ 13.3%	**Case (%) 14.7–15.8%**	**P-value**	**Control (%) ≤ 13.3%**	**Case (%) > 15.8**	**P-value**
AKI	423 (8.9)	397 (8.4)	0.98	255 (8.2)	284 (9.2)	0.24
Thirty-day readmission	480 (10.1)	580 (12.2)	0.001	353 (11.4)	462 (14.9)	<0.001
LOS (median [IQR])	6.5 [1–7]	7.1 [1–7]	0.56	6.9 [1–7]	8.1 [1–8]	0.72
n TOTAL	4729	4729	NA	3097	3097	NA

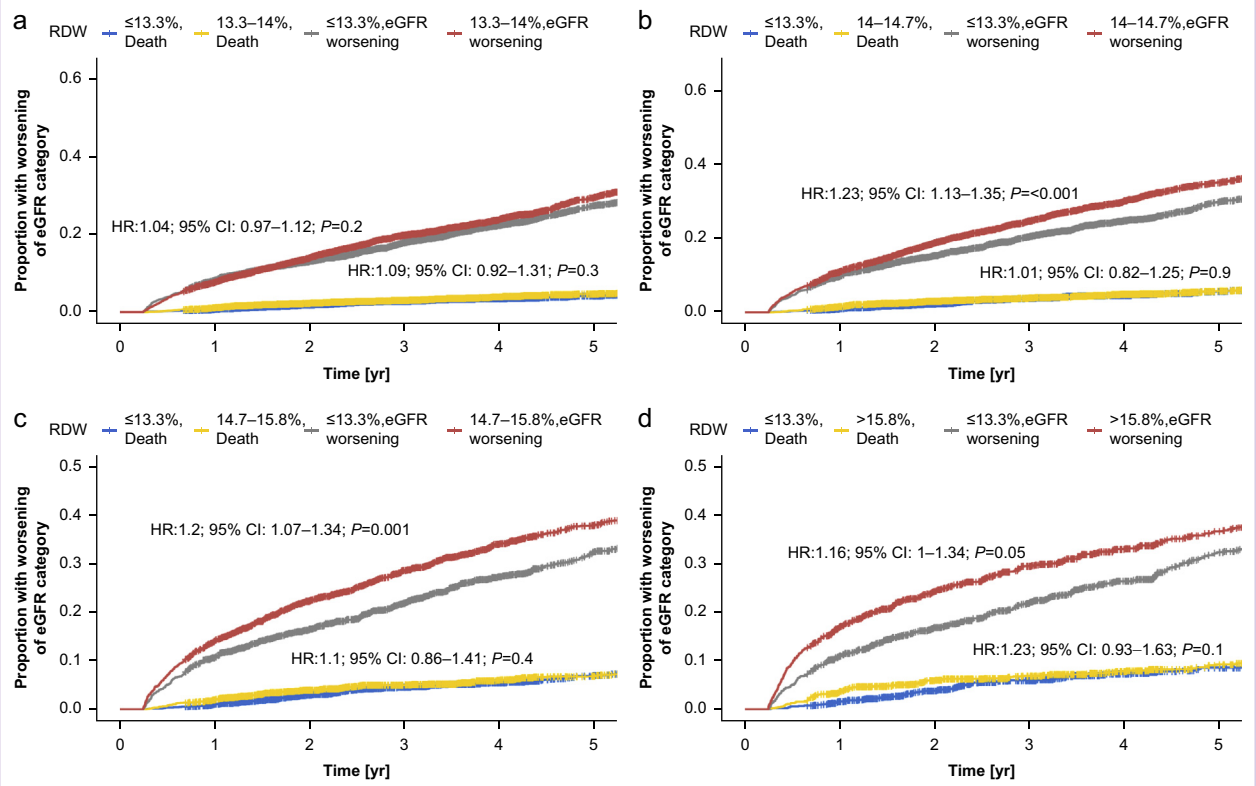

Fig 3. Competing risk analysis, shows both death (blue/yellow lines) and worsening of eGFR category (red/grey lines) amongst group of patients with elevated RDW (yellow/red) of (a) RDW 13.3–14%, (b) RDW 14–14.7%, (c) RDW 14.7–15.8%, and (d) RDW >15.8%, compared with a propensity score-matched (blue/grey) group with normal RDW ≤13.3%. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; RDW, red cell distribution width.

disease found a reduction in their RDW after exercise training and negative correlation was observed between RDW and peak performance.[10,31] These findings suggest that RDW is a modifiable biomarker for adverse outcomes after operation and could be used for risk stratification and to monitor preoperative optimisation.

Key strengths of this study include a large sample size with long extensive follow-up data from a nationwide laboratory database, non-biased inclusion criteria, and adjustment for confounders and competing events.

A key limitation of this study is its single-centre design, which is mediated by the inclusion of an entire population. Data were not available for all individuals leading to exclusions, limiting the statistical power of this study. Furthermore, the low matching rate for higher RDW groups resulted in loss of statistical signal of worsening of eGFR category, especially

considering the increased mortality in this group.[10] Other limitations include lack of preoperative blood transfusion data, not shown to skew RDW measurement or its association with mortality,[11,32,33] and data for different haemoglobin production cofactors such as iron, B12, and folate.[10] Lack of data on albuminuria limited the possibility of further assessment of decline in kidney function,[26] and a more complete assessment of CKD progression.[18] Given the relatively wide reference range of RDW and its dependency on age, gender, and ethnicity, our findings are not generalisable and might not necessarily be transferable to all patient populations.

Conclusions

There is an association between elevated preoperative RDW and postoperative worsening of long-term kidney function that might be mediated by chronic inflammatory state, impaired microvascular flow, or uncaptured confounding. Future studies should focus on better understanding underlying mechanisms and how this marker could be used for risk stratification and optimisation of perioperative outcomes.

Authors' contributions

Study design: all authors
Data analysis: HBO, MIS
Interpretation of data and results: HBO, MIS, SK, MKM, OSI, TEL
Drafting of the manuscript: HBO, MIS
Critical revision of manuscript: all authors

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Declarations of interest

The authors declare that they have no conflicts of interest.

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