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Clinical Investigation

CLINICAL INVESTIGATION

Associations between perioperative fluid management and patient outcomes: a multicentre retrospective study

Timothy E. Miller[1], Monty Mythen[2], Andrew D. Shaw[3], Seungyoung Hwang[4], Apeksha V. Shenoy[4], Michael Bershad[5] and Charles Hunley[6,*]

[1]Department of Anesthesiology, Duke University School of Medicine, Durham, NC, USA, [2]University College London Hospitals, National Institute for Health Research, Biomedical Research Centre, London, UK, [3]Department of Anesthesiology and Pain Medicine, University of Alberta, Edmonton, AB, Canada, [4]Department of Health Economics and Outcomes Research, Boston Strategic Partners, Inc., Boston, MA, USA, [5]Global Health Economics & Reimbursement, Edwards Lifesciences, Irvine, CA, USA and [6]Department of Critical Care Medicine, Orlando Regional Medical Center, Orlando, FL, USA

*Corresponding author. E-mail: charles.hunley@orlandohealth.com

Abstract

Background: Postoperative complications increase hospital length of stay and patient mortality. Optimal perioperative fluid management should decrease patient complications. This study examined associations between fluid volume and noncardiac surgery patient outcomes within a large multicentre US surgical cohort.
Methods: Adults undergoing noncardiac procedures from January 1, 2012 to December 31, 2017, with a postoperative length of stay ≥24 h, were extracted from a large US electronic health record database. Patients were segmented into quintiles based on recorded perioperative fluid volumes with Quintile 3 (Q3) serving as the reference. The primary outcome was defined as a composite of any complications during the surgical admission and a postoperative length of stay ≥7 days. Secondary outcomes included in-hospital mortality, respiratory complications, and acute kidney injury.
Results: A total of 35 736 patients met the study criteria. There was a U-shaped pattern with highest (Q5) and lowest (Q1) quintiles of fluid volumes having increased odds of complications and a postoperative length of stay ≥7 days (Q5: odds ratio [OR] 1.51 [95% confidence interval {CI}: 1.30–1.74], $P<0.001$; Q1: OR 1.20 [95% CI: 1.04–1.38], $P=0.011$) compared with Q3. Patients in Q5 had greater odds of more severe acute kidney injury compared with Q3 (OR 1.52 [95% CI: 1.22–1.90]; $P<0.001$) and respiratory complications (OR 1.44 [95% CI: 1.17–1.77]; $P<0.001$).
Conclusions: Both very high and very low perioperative fluid volumes were associated with an increase in complications after noncardiac surgery.

Keywords: acute kidney injury; in-hospital mortality; noncardiac surgery; outcome; patient complications; perioperative fluid management; postoperative length of stay; respiratory complications

Editor's key points

- Excessively high or low perioperative i.v. fluid volumes are likely to cause harm.
- This real-world study across 119 US hospitals found increased risk of complications in patients receiving much higher or much lower i.v. fluid volumes during and after surgery.
- Patients receiving high fluid volumes had significantly greater odds of more severe acute kidney injury and respiratory complications.
- Optimal patient- and procedure-specific i.v. fluid volumes should be achievable.
- Fluid management protocols may potentially benefit and expedite patient recovery.

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Postoperative complications, including minor complications, increase readmissions and hospital length of stay (LOS), and negatively impact long-term survival rates.[1–3] These outcomes represent a healthcare burden for patients and an economic burden to payers and hospitals. Thus, minimising postoperative complications both improves clinical outcomes and accrues economic benefits.[4]

Perioperative fluid management is identified as one of the key elements to impact surgical outcomes.[5,6] Hypovolaemia leads to low cardiac output and decreased tissue perfusion,[7,8] whereas hypervolaemia leads to weight gain, tissue oedema, ileus, and possibly mortality.[9,10] Many clinical trials and retrospective studies have analysed the relationship between intra- and perioperative fluid volumes and patient outcomes. A hospital registry study, across three hospitals, identified that both liberal and restrictive volumes were associated with higher odds of mortality and acute kidney injury (AKI).[11] Another retrospective study determined that high fluid volume usage on the day of surgery led to increased LOS and higher total costs in patients who underwent rectal, colon, or hip and knee surgeries.[9] A single-site retrospective study determined that postoperative complications were independently related to postoperative fluid volumes in patients who underwent elective gastrointestinal (GI) surgery.[12]

The aforementioned retrospective studies were carried out in patient populations limited either by lack of clinical data,[13] sample size,[12] region,[11] or surgical procedures,[9] and the outcomes analysed were restricted to one or two major organ systems.[9,11] Therefore, in the current study, we chose to examine a large patient cohort undergoing a diverse set of surgical procedures from multiple hospitals across the USA. We tested the hypothesis that patient receipt of higher or lower quintiles of perioperative fluid volume may be associated with poorer clinical outcomes compared with patients who received moderate fluid volumes.

Methods

Data source

We conducted a retrospective analysis using the de-identified Cerner Health Facts® electronic health record (EHR) database (Kansas City, MO, USA) providing longitudinal, clinical, and administrative patient data from hospitals and clinics. In advance, our study was determined to be exempt from institutional review board (IRB) review by Western IRB (Puyallup, WA, USA) after a review of our statistical analysis plan.

Patient population

Adults (≥18 yr of age) undergoing select noncardiac surgeries[14] (Supplementary Table S1) between January 1, 2012 and December 31, 2017, with a postoperative LOS ≥24 h who received a minimum 500 ml of i.v. fluid during a predetermined exposure window (6 h before surgery to 24 h post-surgery), were selected. After an independent review by the four clinician authors, noncardiac surgeries[14] were selected based on patient requirement for fluid therapy during the procedure and surgical duration.

Patients who underwent cardiac surgery or Caesarean section were excluded from this study. Patients were also excluded if (i) any surgery[14] (Supplementary Table S1) appeared in a patient record within 4 weeks before the index surgical encounter, (ii) postoperative stay was <24 h or >180 days, (iii) they received dextran or hypertonic saline during the visit, (iv) records lacked ≥1 month of data before the surgical encounter, and (v) records lacked gender or diagnosis/medication information. Patients with data quality issues, such as clinically improbable fluid volume or surgery duration, were also excluded. Based on the distribution, patients with fluid volume or surgery duration in the highest 1% were omitted from the analysis.

Exposure(s)

Fluid exposure was calculated between 6 h before surgery and 24 h post-surgery. All fluid volumes administered within this time period, including crystalloids and colloids, were defined as 'total fluid volume' received per patient. Blood and blood product volumes were not included because of their unavailability in the database. However, blood transfusion was identified via procedure codes and added as a covariate during modelling (see Statistical analysis). Patients were divided into five equal quintiles (Q) based on total perioperative fluid volume for a granular comparison and to also maintain a reasonable *N* per group: lowest (Q1), low (Q2), moderate (Q3), high (Q4), and highest (Q5).

Outcome measures

The primary outcome was a composite of complications during the surgical visit paired with a postoperative LOS of ≥7 days (e.g. the complication would not be counted for an LOS <7 days). Complications for major organ systems were defined using International Classification of Diseases (ICD) 9/10 medical codes (Supplementary Table S2). A review of patient history up to 6 months before surgery was conducted to ensure that chronic complications (Supplementary Table S2) within the composite were newly developed. If patient records contained one of the chronic conditions before admission, the patient was excluded for that particular condition within the composite complications.

Complications included (i) infections (urinary tract infection, wound infection, system sepsis/septic shock, and other infectious diseases), (ii) GI (nausea and vomiting, ileus [paralytic or functional], acute bowel obstruction, GI bleeding, abdominal compartment syndrome, hepatic dysfunction, pancreatitis, and other GI diseases), (iii) cardiovascular (deep venous thrombosis, pulmonary embolism, myocardial ischaemia or infarction, arrhythmia [includes cardiac arrest], shock, cerebrovascular accident/stroke, heart failure, and infarction of GI tract), (iv) renal (renal insufficiency or failure, AKI, and renal replacement therapy [RRT]), and (v) respiratory (pneumonia, mechanical ventilation, respiratory failure or acute respiratory distress syndrome [ARDS], and pleural effusion).

Three secondary outcomes were defined: in-hospital mortality, respiratory complications, and AKI. In-hospital mortality was identified by the discharge status of 'deceased' during the hospital index visit. Respiratory complications were identified by ICD 9/10 codes (Supplementary Table S2). AKI that developed 7 days postoperatively was analysed separately for patients with and without a chronic kidney disease/end-stage renal disease (CKD/ESRD) diagnosis code (Supplementary Table S2) in the 6 months before surgery start. Serum creatinine (SCr) readings were utilised to identify the presence and stage of AKI via the Post-operative Kidney Disease Improving Global Outcomes (KDIGO, 2012) guidelines

Table 1 Patient characteristics for the overall cohort and by quintile of fluid volume. ACE, angiotensin-converting enzyme; APS, acute physiology score; ARB, angiotensin II receptor blocker; IQR, inter-quartile range; SD, standard deviation. Because of rounding, categories will not always add to 100%. APS includes physiology variables. *At index hospital visit. †Includes procedures on skin subcutaneous tissue fascia and breast. ‡Includes other male genital procedures. ¶Excluding bone marrow corneal and kidney. §Before index hospital visit. ||Day before and day of surgery. #Within 24 h before surgery. **Between admission and start of surgery. ††Fluid exposure window (6 h preoperative to 24 h postoperative). ‡‡From admission to the day after surgery. ¶¶From admission to the day of surgery.

	Overall cohort (*N*=35 736), *n* (%)	Quintile of fluid volume				
		Q1 (very low; *N*=7147), *n* (%)	Q2 (low; *N*=7148), *n* (%)	Q3 (moderate; *N*=7147), *n* (%)	Q4 (high; *N*=7147), *n* (%)	Q5 (very high; *N*=7147), *n* (%)
Patient characteristics						
Age (yr), median (IQR)*	62 (20)	62 (21)	63 (20)	62 (20)	63 (20)	61 (20)
Sex*						
Female	21 536 (60.3)	4199 (59.8)	4210 (58.9)	4365 (61.1)	4433 (62.0)	4329 (60.6)
Male	14 200 (39.7)	2948 (41.2)	2937 (41.1)	2783 (38.9)	2714 (38.0)	2818 (39.4)
Race*						
Caucasian	28 022 (78.4)	5426 (75.9)	5697 (79.7)	5686 (79.6)	5593 (78.3)	5620 (78.6)
African American	5254 (14.7)	1151 (16.1)	941 (13.2)	893 (12.5)	1131 (15.8)	1138 (15.9)
Other	2103 (5.9)	450 (6.3)	438 (6.1)	498 (7.0)	374 (5.2)	343 (4.8)
Unknown	357 (1.0)	120 (1.7)	71 (1.0)	71 (1.0)	49 (0.7)	46 (0.6)
Admission type*						
Emergency	6384 (17.9)	1797 (25.1)	1352 (18.9)	941 (13.2)	1046 (14.6)	1248 (17.5)
Urgent	2027 (5.7)	511 (7.1)	392 (5.5)	343 (4.8)	383 (5.4)	398 (5.6)
Elective	26 872 (75.2)	4666 (65.3)	5336 (74.7)	5710 (79.9)	5680 (79.5)	5480 (76.7)
Unknown	453 (1.3)	173 (2.4)	67 (0.9)	154 (2.2)	38 (0.5)	21 (0.3)
Surgery type*						
Orthopaedic	17 299 (48.4)	3257 (45.6)	3790 (53.0)	3521 (49.3)	3679 (51.5)	3052 (42.7)
Gastrointestinal	6377 (17.8)	1179 (16.5)	1098 (15.4)	1088 (15.2)	1182 (16.5)	1830 (25.6)
Gynaecological	2853 (8.0)	446 (6.2)	439 (6.1)	677 (9.5)	620 (8.7)	671 (9.4)
Urological	2317 (6.5)	423 (5.9)	490 (6.9)	464 (6.5)	456 (6.4)	484 (6.8)
Vascular	1689 (4.7)	438 (6.1)	331 (4.6)	279 (3.9)	265 (3.7)	376 (5.3)
Neurosurgery	1438 (4.0)	403 (5.6)	306 (4.3)	318 (4.4)	255 (3.6)	156 (2.2)
Thoracic	1247 (3.5)	341 (4.8)	272 (3.8)	215 (3.0)	222 (3.1)	197 (2.8)
Mastectomy/skin graft†	1130 (3.2)	305 (4.3)	174 (2.4)	280 (3.9)	184 (2.6)	187 (2.6)
Endocrine	705 (2.0)	214 (3.0)	125 (1.7)	165 (2.3)	112 (1.6)	89 (1.2)
Prostatectomy‡	568 (1.6)	70 (1.0)	96 (1.3)	134 (1.9)	167 (2.3)	101 (1.4)
Organ transplant¶	113 (0.3)	71 (1.0)	26 (0.4)	7 (0.1)	5 (0.1)	4 (0.1)
Surgery duration (min), mean (SD)*	146.0 (82.6)	145.8 (86.0)	139.2 (83.1)	139.8 (77.2)	139.3 (77.5)	165.9 (85.9)
Payer*						
Medicare	13 969 (39.1)	3335 (46.7)	3302 (46.2)	2906 (40.7)	2498 (35.0)	1928 (27.0)
Medicaid	2399 (6.7)	562 (7.9)	569 (8.0)	559 (7.8)	387 (5.4)	322 (4.5)
Commercial	9211 (25.8)	1970 (27.6)	2137 (29.9)	2287 (32.0)	1598 (22.4)	1219 (17.1)
Other	3113 (8.7)	819 (11.5)	678 (9.5)	554 (7.8)	640 (9.0)	422 (5.9)
Unknown	7044 (19.7)	461 (6.5)	461 (6.4)	842 (11.8)	2024 (28.3)	3256 (45.6)
Index year*						
2012	2749 (7.7)	600 (8.4)	377 (5.3)	472 (6.6)	619 (8.7)	681 (9.5)
2013	9241 (25.9)	1605 (22.5)	1475 (20.6)	1756 (24.6)	2113 (29.6)	2292 (32.1)
2014	10 819 (30.3)	2087 (29.2)	2010 (28.1)	2035 (28.5)	2190 (30.6)	2497 (34.9)
2015	7893 (22.1)	1684 (23.6)	1990 (27.8)	1732 (24.2)	1378 (19.3)	1109 (15.5)
2016	3912 (10.9)	840 (11.8)	1005 (14.1)	866 (12.1)	704 (9.9)	497 (7.0)
2017	1122 (3.1)	331 (4.6)	290 (4.1)	287 (4.0)	143 (2.0)	71 (1.0)
Charlson Comorbidity Index, mean (SD)§	2.0 (2.4)	2.3 (2.6)	2.0 (2.4)	1.8 (2.3)	1.8 (2.2)	2.0 (2.3)
Elixhauser comorbidities*						
Blood loss anaemia	468 (1.3)	111 (1.6)	88 (1.2)	72 (1.0)	79 (1.1)	118 (1.7)
Fluid and electrolyte disorders	6333 (17.7)	1389 (19.4)	1230 (17.2)	1020 (14.3)	1126 (15.8)	1568 (21.9)
Weight loss	1558 (4.4)	378 (5.3)	315 (4.4)	230 (3.2)	235 (3.3)	400 (5.6)
APS score, mean (SD)||	25.2 (13.2)	24.2 (13.8)	23.9 (13.4)	23.8 (12.6)	25.8 (12.5)	28.3 (13.3)
Medications (yes)						
Beta blockers#	2234 (6.3)	589 (8.2)	442 (6.2)	349 (4.9)	407 (5.7)	447 (6.3)
ACE inhibitors or ARBs#	1043 (2.9)	236 (3.3)	203 (2.8)	168 (2.4)	221 (3.1)	215 (3.0)
Calcium channel blockers#	963 (2.7)	229 (3.2)	222 (3.1)	177 (2.5)	178 (2.5)	157 (2.2)
Diuretics**	1918 (5.4)	517 (7.2)	406 (5.7)	263 (3.7)	342 (4.8)	390 (5.5)
Inotropes#	1379 (3.9)	241 (3.4)	244 (3.4)	291 (4.1)	346 (4.8)	257 (3.6)

Continued

Table 1 Continued

	Overall cohort (N=35 736), n (%)	Quintile of fluid volume				
		Q1 (very low; N=7147), n (%)	Q2 (low; N=7148), n (%)	Q3 (moderate; N=7147), n (%)	Q4 (high; N=7147), n (%)	Q5 (very high; N=7147), n (%)
Vasopressors[#]	2831 (7.9)	478 (6.7)	564 (7.9)	508 (7.1)	562 (7.9)	719 (10.1)
Antibiotics[#]	28 441 (79.6)	4964 (69.5)	5630 (78.8)	5866 (82.1)	5944 (83.2)	6037 (84.5)
Starches[††]	1036 (2.9)	165 (2.3)	124 (1.7)	117 (1.6)	204 (2.9)	426 (6.0)
Albumin[††]	3364 (9.4)	896 (12.5)	572 (8.0)	411 (5.8)	561 (7.8)	924 (12.9)
Procedures						
Blood transfusion[‡‡]	2881 (8.1)	546 (7.6)	507 (7.1)	438 (6.1)	548 (7.7)	842 (11.8)
Early ventilation[¶¶]	689 (1.9)	180 (2.5)	118 (1.7)	78 (1.1)	92 (1.3)	221 (3.1)

framework[15] (using criteria for SCr increase over baseline [defined as the value closest to surgery in the 6 months prior; if unavailable, SCr on surgery day was used] and with respect to SCr values within 48 h). Patients were excluded from the AKI outcome analysis when SCr readings were not available within the specified time frames, RRT/dialysis medical codes were present within 6 months before surgery, AKI diagnosis codes were present within the month before start of surgery (Supplementary Table S2), or KDIGO AKI identified between hospital admission and surgery. We also examined mechanical ventilation separately as an exploratory outcome via ICD 9/10 codes (Supplementary Table S2).

Statistical analysis

Patient baseline characteristics were summarised via counts and percentages for binary or categorical variables, and with means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous variables. Multiple logistic regression quantified the relationship between the fluid volume quintiles and the binary outcomes (complications with a postoperative LOS of ≥7 days, in-hospital mortality, and respiratory complications). Proportional odds logistic regression was used to evaluate AKI as an ordinal outcome, with Stages II and III combined representing 'more severe AKI'. The χ^2 test was used to assess the proportional odds assumptions. Both logistic regression models were adjusted for within-hospital clustering by using a robust variance estimator to account for potential within-cluster correlations amongst patients treated at the same hospital. The associations between fluid quintiles and outcomes were assessed with odds ratios (ORs) and associated 95% confidence intervals (CIs). A meta-analysis[16] of several trials has shown that traditionally administered fluid volumes (liberal) may produce poorer outcomes in patients. The Restrictive Versus Liberal Fluid Therapy in Major Abdominal Surgery (RELIEF) study[17] recently demonstrated that a restrictive regimen may not always be beneficial. Hence, we chose the moderate quintile Q3 as a reference for the analyses in line with our study hypothesis. Tables 1 and 2 list all covariates included in the models: patient characteristics, such as age, sex, race, admission type, payer, surgery type, surgery duration, year of surgery, receipt of relevant medications over specified time frames, and procedures (blood transfusion and early mechanical ventilation), and hospital characteristics, such as bed size, teaching status, location (urban *vs* rural), and census region. Comorbidities were evaluated using the Charlson Comorbidity Index,[18] relevant Elixhauser comorbidities (blood loss anaemia, fluid and electrolyte disorders, and weight loss), and the acute physiology score of the Acute Physiology and Chronic Health Evaluation III to account for case severity.[19] All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) with alpha at 0.05.

Results

Study cohort and patient characteristics

A total of 35 736 patients in 119 hospitals met the study selection criteria (Fig. 1). The median (IQR) age of the cohort was 62 (20): 60.3% (*n*=21 536) were females and 78.4% were Caucasian (*n*=28 022). The average (SD) surgery duration was 146 (83) min. The mean (SD) fluid volume received during the exposure window was 2290 (1283) ml. The fluid volume received for each of the five quintiles was as follows: Q1: lowest (*n*=7147): 500–1191 ml; Q2: low (*n*=7148): 1191–1775 ml; Q3: moderate (*n*=7147): 1775–2333 ml; Q4: high (*n*=7147): 2333–3216 ml; and Q5: highest (*n*=7147): 3216–7932 ml.

Primary outcome

Rates of complications, overall and by category, in the cohort were as follows: (i) ≥1 complications: 4047 patients (11.3%); (ii) GI: 1871 (5.2%); (iii) respiratory: 1863 (5.2%); (iv) cardiovascular: 1857 (5.2%); (v) infection: 1817 (5.1%), and (vi) renal: 1363 (3.8%). Details of all outcomes according to quintile of fluid volume are included in Table 3. Rates of mutually exclusive complications are shown in Figure 2 by type and quintile of fluid volume.

Adjusted outcomes showed that increasing or decreasing fluid volumes (Q1, Q4, and Q5) were significantly associated with increased odds of having one or more complications (Q5: OR 1.51 [95% CI: 1.30–1.74], *P*<0.001; followed by Q1: OR 1.20 [95% CI: 1.04–1.38], *P*=0.011) (Fig. 3). Adjusted odds by surgery type are in Supplementary Table S3.

Secondary outcomes

The observed rate of post-surgical mortality in the study cohort was 0.7% (*n*=268). Adjusted analysis showed non-moderate fluid volumes (all quintiles except Q3) tended to show higher odds of mortality, but these were not statistically significant.

Respiratory complications occurred in 5.2% (*n*=1863) of patients. Odds of respiratory complications were significantly higher for patients in Q5 (OR 1.44 [95% CI: 1.17–1.77]; *P*<0.001) compared with those in Q3 (Fig. 3). We also examined mechanical ventilation as a separate outcome, with ORs in Supplementary Table S4.

Table 2 Hospital characteristics for the overall cohort and by quintile of fluid volume. Because of rounding, categories will not always add to 100%. *At index hospital visit.

	Overall cohort (N=35 736), n (%)	Quintile of fluid volume				
		Q1 (very low; N=7147), n (%)	Q2 (low; N=7148), n (%)	Q3 (moderate; N=7147), n (%)	Q4 (high; N=7147), n (%)	Q5 (very high; N=7147), n (%)
Hospital characteristics						
Bed size*						
<100	3114 (8.7)	663 (9.3)	822 (11.5)	632 (8.8)	559 (7.8)	438 (6.1)
100–199	1668 (4.7)	597 (8.4)	316 (4.4)	244 (3.4)	257 (3.6)	254 (3.6)
200–299	10 583 (29.6)	1679 (23.5)	1980 (27.7)	1872 (26.2)	2386 (33.4)	2666 (37.3)
300–499	6377 (17.8)	1105 (15.5)	1216 (17.0)	1480 (20.7)	1451 (20.3)	1125 (15.7)
500+	13 994 (39.2)	3103 (43.4)	2813 (39.4)	2920 (40.9)	2494 (34.9)	2664 (37.3)
Teaching status*						
Yes	27 832 (77.9)	5539 (77.5)	5407 (65.6)	5622 (78.7)	5465 (76.5)	5799 (81.1)
No	7904 (22.1)	1608 (22.5)	1740 (24.3)	1526 (21.4)	1682 (23.5)	1348 (18.9)
Location*						
Urban	32 389 (90.6)	6015 (84.2)	6460 (90.4)	6665 (93.2)	6584 (92.1)	6665 (93.3)
Rural	3347 (9.4)	1132 (15.8)	687 (9.6)	483 (6.8)	563 (7.9)	482 (6.7)
Census region*						
Midwest	5872 (16.4)	1096 (15.3)	1027 (14.4)	1143 (16.0)	1309 (18.3)	1297 (18.1)
Northeast	17 458 (48.9)	2688 (37.6)	3209 (44.9)	3717 (52.0)	3688 (51.6)	4156 (58.2)
South	8412 (23.5)	2126 (29.7)	1784 (25.0)	1548 (21.7)	1649 (23.1)	1305 (18.3)
West	3994 (11.2)	1237 (17.3)	1127 (15.8)	740 (10.4)	501 (7.0)	389 (5.4)

We identified 26 514 patients evaluable for AKI without CKD/ESRD within 6 months before surgery. Of this cohort, 1184 (4.5%) patients developed AKI Stage I or higher. Patients in Q5 had 52% greater odds of exhibiting more severe AKI (OR 1.52 [95% CI: 1.22–1.90]; $P<0.001$) than patients in Q3, whereas those in Q4 had 26% greater odds (OR 1.26 [95% CI: 1.02–1.56]; $P=0.031$) (Fig. 3).

Of the 2082 patients who satisfied the criteria for AKI evaluation and with a history of CKD/ESRD within 6 months before surgery, 401 patients (19.3%) experienced AKI. Patients in the first, fourth, and fifth quintiles tended to have increased

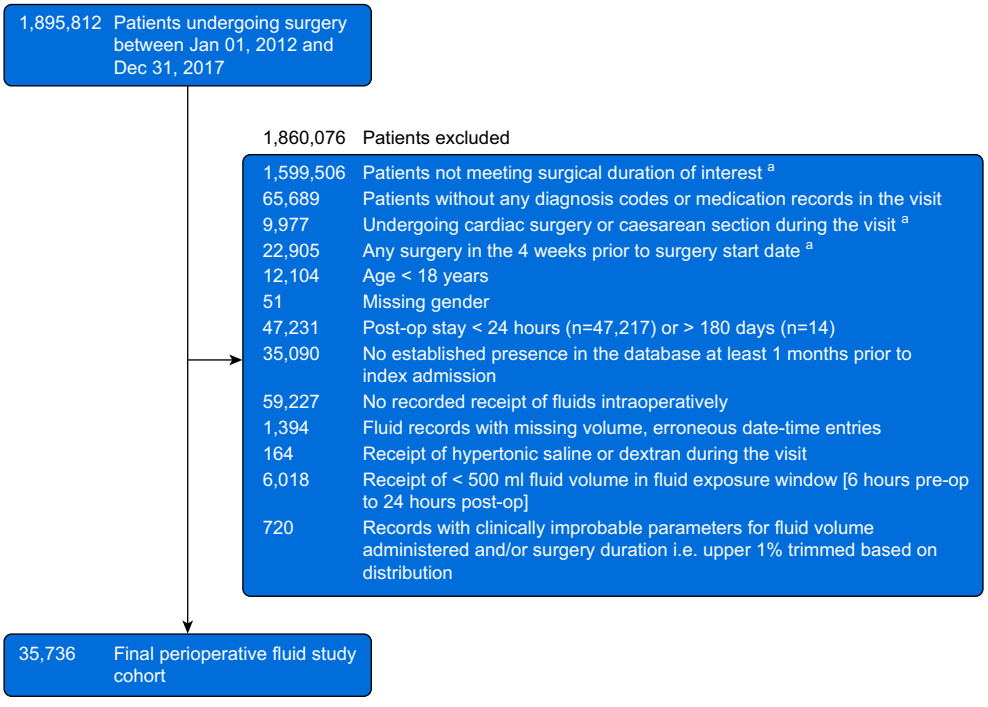

Fig 1. Patient selection flow diagram. *See Supplementary Table S1 for the complete list of medical codes.

Table 3 Descriptive statistics for all outcomes: overall cohort and by quintile of fluid volume. AKI, acute kidney injury; CKD, chronic kidney disease; ESRD, end-stage renal disease; LOS, length of stay. *A subset of patients was evaluated for AKI based on the selection criteria outlined in Methods.

	Overall cohort (N=35 736), n (%)	Quintile of fluid volume				
		Q1 (very low; N=7147), n (%)	Q2 (low; N=7148), n (%)	Q3 (moderate; N=7147), n (%)	Q4 (high; N=7147), n (%)	Q5 (very high; N=7147), n (%)
Primary outcome						
Complications with a postoperative LOS ≥7 days	4047 (11.3)	982 (13.7)	739 (10.3)	545 (7.6)	662 (9.3)	1119 (15.7)
Secondary outcomes						
In-hospital mortality	268 (0.7)	68 (1.0)	52 (0.7)	29 (0.4)	45 (0.6)	74 (1.0)
Respiratory complications	1863 (5.2)	438 (6.1)	345 (4.8)	238 (3.3)	292 (4.1)	550 (7.7)
AKI stages (no history of CKD/ESRD]*	N=26 514	N=4909	N=5274	N=5541	N=5322	N=5468
0	25 330 (95.5)	4680 (95.3)	5034 (95.4)	5361 (96.8)	5099 (95.8)	5156 (94.3)
1	1032 (3.9)	206 (4.2)	201 (3.8)	157 (2.8)	200 (3.8)	268 (4.9)
2	126 (0.5)	19 (0.4)	35 (0.7)	18 (0.3)	19 (0.4)	35 (0.6)
3	26 (0.1)	4 (0.1)	4 (0.1)	5 (0.1)	4 (0.1)	9 (0.2)
AKI stages (history of CKD/ESRD]*	N=2082	N=416	N=423	N=376	N=422	N=445
0	1681 (80.7)	336 (80.8)	352 (83.2)	318 (84.6)	347 (82.2)	328 (73.7)
1	350 (16.8)	74 (17.8)	62 (14.7)	51 (13.6)	61 (14.5)	102 (22.9)
2	15 (0.7)	1 (0.2)	3 (0.7)	1 (0.3)	6 (1.4)	4 (0.9)
3	36 (1.7)	5 (1.2)	6 (1.4)	6 (1.6)	8 (1.9)	11 (2.5)

odds of developing more severe AKI (Q1: OR 1.31 [95% CI: 0.85–2.04], P=0.22; Q4: 1.23 [95% CI: 0.80–1.89], P=0.34; Q5: 1.22 [95% CI: 0.79–1.89], P=0.36) than patients in Q3, although the differences were not statistically significant (Fig. 3). Supplementary Table S4 provides additional adjusted odds, including those for developing any AKI (Stages I, II, and III combined) with respect to fluid quintiles. Unadjusted odds for all outcomes are in Supplementary Table S5.

Discussion

In an analysis of 35 637 noncardiac surgery patients from an EHR database, we found a U-shaped association between perioperative fluid volumes and complications; the 'lowest' and 'highest' fluid groups had increased odds of complications. Patients receiving the most fluid were also independently associated with AKI and respiratory complications.

This study adds to existing published literature, as it analyses a uniquely comprehensive list of complications; has a large cohort drawing from 119 individual hospitals, including a sizable percentage (23.6%) of emergency/urgent cases; and has a wide set of major noncardiac procedures across all surgical risk categories. By evaluating the association of real-world prescribed fluid volumes in incremental variations, this study demonstrates an association with adverse clinical outcomes. Furthermore, with the evolution of noncardiac surgical and fluid management protocols over time, our study provides insights into the latest practices by analysing data from recent years.

Both hypervolaemia and hypovolaemia are detrimental to patients' health.[7–10] The optimal fluid volumes required to reduce fluid-related complications have remained elusive. Our study shows a U-shaped association between fluid volumes administered and composite complications. We limited this outcome to patients with a postoperative hospital stay of ≥7 days to account only for those requiring increased hospital resources. Two older trials[20,21] (2005 and 2009) evaluated a composite of complications to infer that patients in the liberal fluid volume group experienced higher rates of complications compared with those given restrictive fluid volumes. These trials solely evaluated two thresholds, restrictive *vs* liberal, rather than of a spectrum of fluid volumes, and were limited by small patient cohorts and specific surgery types. Another retrospective analysis[9] observed a U-shaped association between fluid volumes and postoperative ileus amongst patients who underwent colorectal or orthopaedic procedures. A hospital registry study[11] of noncardiac surgery patients showed a U-shaped association between fluid volumes and renal complications, and greater odds of respiratory complications in patients receiving liberal volumes. Although these studies[9,11] looked at the effect of incremental fluid volumes, the complications were limited to one or two organ systems. In comparison, complications selected in our analysis were five-fold: infectious, GI, cardiovascular, renal, and respiratory, and focused only on those patients with a postoperative LOS at a certain threshold (≥7 days).

Our in-hospital mortality results, although not significant, exhibited a U-shaped trend with respect to fluid volumes. A meta-analysis[16] (2012) evaluating binary fluid thresholds, liberal *vs* restrictive, favoured restrictive fluid volumes for improved mortality, but did not achieve significance. The RELIEF trial[17] showed that patients with restrictive fluid volumes had a poorer outcome (composite of 30 day mortality or septic complications) than the liberal fluid group aimed at zero balance, but the difference was not significant. It is important to note that the fluid volumes labelled 'restrictive' change widely with each study and are not directly comparable with our volume quintiles (Q1: lowest; Q5: highest). However, in a recent study by Shin and colleagues,[11] mortality was higher for non-moderate fluid volumes, in agreement with our results.

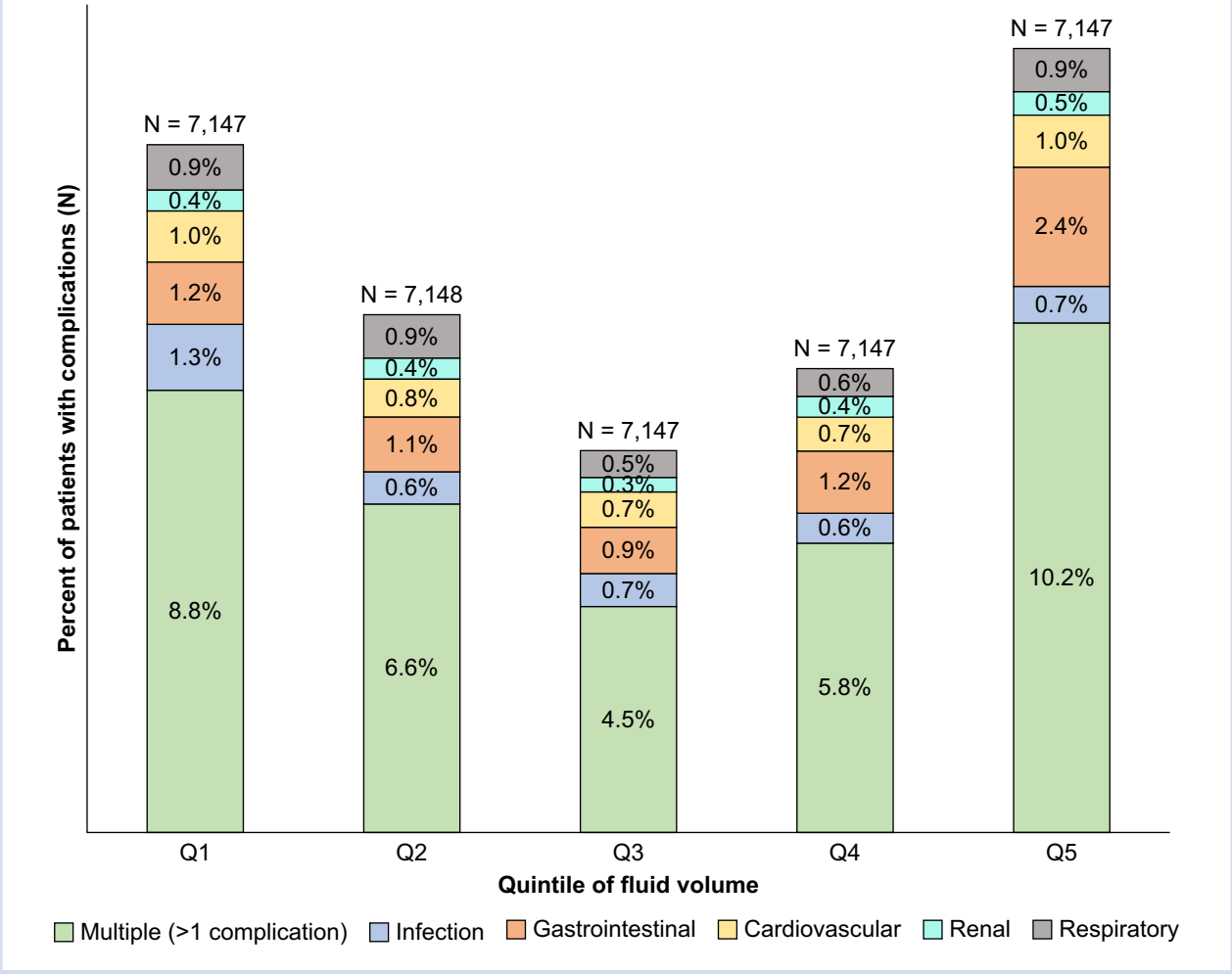

Fig 2. Complication rates by type and quintile of fluid volume. Distribution of patients by mutually exclusive complication types (infection, cardiovascular, gastrointestinal, renal, respiratory, and multiple [more than one complication]) and quintile of fluid volume.

This study looked at 30 day mortality, whereas we examined in-hospital mortality.[11]

Our AKI outcomes indicated higher odds of exhibiting more severe AKI in all non-moderate quintiles, but only significantly in Q4–Q5 patients. Hypovolaemia is known to have deleterious effects on the kidney, as it causes renal hypoperfusion, eventually leading to acute tubular necrosis.[22] However, hypervolaemia can also have equally deleterious consequences. Large fluid volumes affect renal uptake and cause creatinine build-up in serum. A rapid increase in SCr can lead to AKI.[15,23,24] The RELIEF trial revealed a higher AKI rate in the 'restrictive' group compared with 'liberal'.[17] However, the RELIEF trial included only major abdominal surgeries. Q5 in our study has the largest share (25.6%) of digestive surgeries compared with the other groups, and both the restrictive (median 3.7 L) and liberal (median 6.1 L) fluid strategies used in RELIEF belong to this quintile in our study. From the perspective of an incremental volume analysis, a recent analysis showed that patients receiving restrictive and liberal volumes developed AKI.[18] The current study takes the analysis one step further, segmenting patients by their kidney status, CKD/ESRD *vs* not, demonstrating a higher rate of AKI amongst patients in the CKD/ESRD group[25] with moderate fluid volumes having the least odds of developing a more severe AKI stage.

As expected, we observed higher odds for respiratory complications at high perioperative fluid volume. High fluid volumes can cause ARDS,[26] pulmonary oedema, or pneumonia.[16] Our results complement the existing understanding of the impact of fluid administration on respiratory complications by demonstrating that patients receiving moderate volumes had a relatively better outcome.

Overall, our study reinforced that low and high fluid volumes are detrimental to patients, as they have greater odds of developing one or more complications with a $\geq$7 day postoperative LOS. Higher fluid volumes were significantly associated with greater odds of respiratory complications and more severe AKI.

This study has several limitations. The Cerner Health Facts® EHR data set does not provide urine volumes; thus, we could not assess patient fluid balance. Therefore, we utilised SCr measurements while evaluating AKI. However, a previously published meta-analysis of cohort studies found no

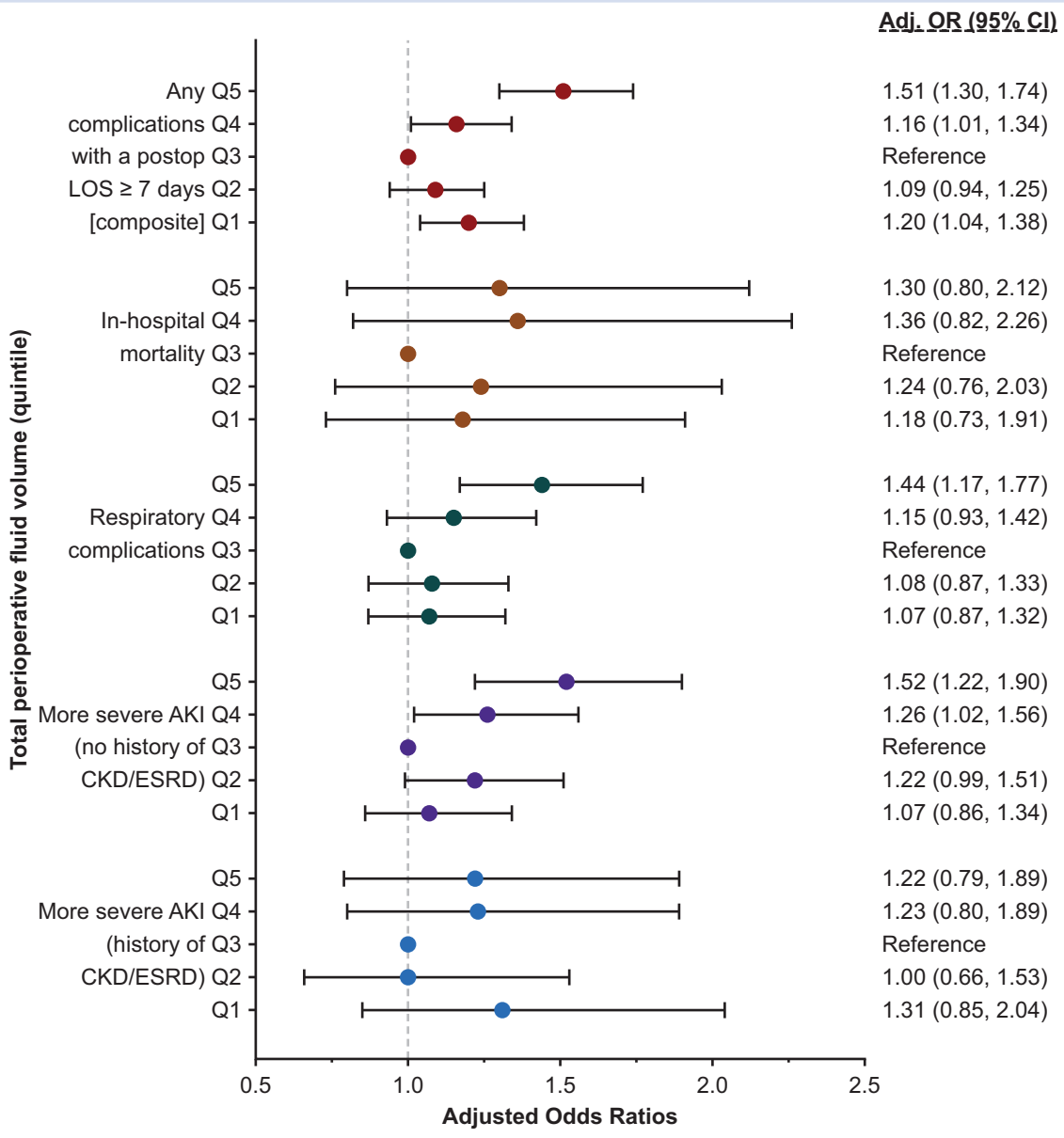

Fig 3. Association of perioperative fluid volume with patient outcomes. The adjusted odds ratios with 95% confidence intervals for all outcomes during the study period are shown. AKI, acute kidney injury; CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; LOS, length of stay; OR, odds ratio.

difference in cohorts that did or did not utilise urine output to define AKI.[27] This study is restricted to i.v. fluid administration and does not account for patient oral hydration. We also could not account for blood and blood product volumes within the total perioperative fluid volume received because of their unavailability in the database. However, we identified transfusions via ICD 9/10 codes. Q5 showed double the transfusion rate of Q3 (11.8% *vs* 6.1%) combined with higher fluid received might indicate blood loss or dilutional effect of excessive fluids. We adjusted all models for transfusion procedures to provide results independent of blood loss. As our study is retrospective, unmeasured confounding is a possibility. Our dependence on ICD codes to identify clinical procedures and complications may be subject to reporting bias, and therefore, treatments/events may be under-reported. However, we expect any over- or under-reporting to occur consistently across institutions, and should have little to no impact on the results. Our study does not examine outcomes post-hospital discharge; for example, our data set did not allow for linkage to the Social Security Index, and therefore, mortality could not be assessed outside the hospital. The associations with mid-to long-term outcomes are unknown. As the data set does not provide patient costs, they could not be analysed. However, this study warrants future studies to investigate potential

economic benefits. Lastly, these study results indicate only an association between fluid volumes and patient outcomes, but cannot determine causality. Randomised trials will be required to confirm if any causal relationship exists.

In conclusion, our study reports an association between non-ideal (too low or too high) perioperative fluid volumes administered and poorer clinical outcomes compared with moderate fluid volume. A closer look at fluid management protocols may potentially benefit and expedite patient recovery. In light of these results, studies are warranted to investigate patient-specific optimal fluid volumes for minimising avoidable complications.

Authors' contributions

Study conception/design: all authors
Data analysis: SH
Data interpretation: all authors
Writing of original draft: AVS
Writing/review/editing of paper: all authors

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Declarations of interest

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Appendix A. Supplementary data

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