Supplemental Online Content

Siegal DM, Belley-Cote EP, Lee SF, et al. Small-volume blood collection tubes to reduce transfusions in intensive care: the STRATUS randomized clinical trial. *JAMA*. doi:10.1001/jama.2023.20820

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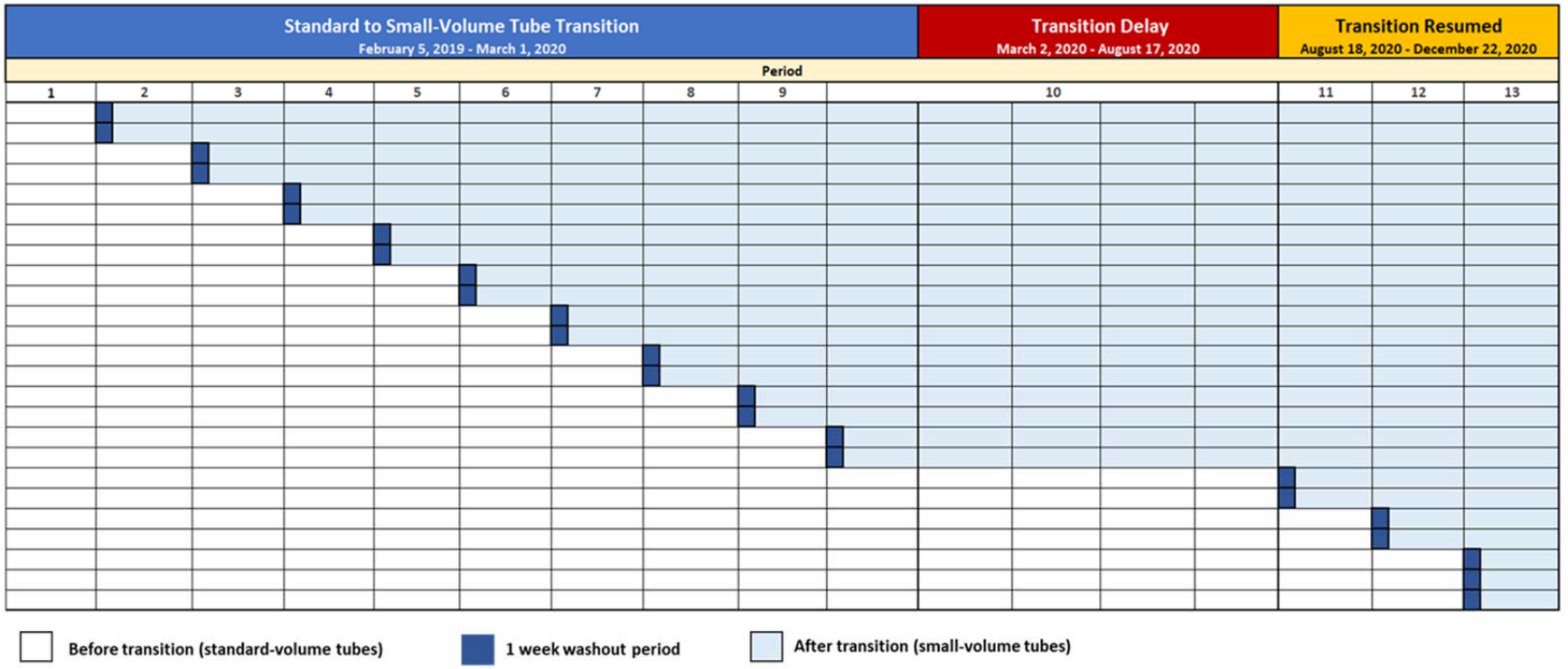
eFigure 1: Study timeline and randomized transition scheme



eFigure 1. Diagram showing the study timeline and sequence of randomized transitions. After a 6-week baseline period during which sites used standard-volume tubes according to routine care, each ICU transitioned randomly from standard-volume tubes (white) to small-volume tubes (light blue) according to a concealed randomization schedule. At 6-week intervals, 2 sites switched to the small-volume tubes. Transitions were followed by a 1-week washout period (dark blue) during which small-volume tubes were used but data were excluded from analysis. Transitions were paused at 7 sites after the onset of the COVID-19 pandemic ("transition delay") during which time all sites uses the allocated tubes and data collection continued. Transitions resumed after a 5-month delay and were completed by all sites.

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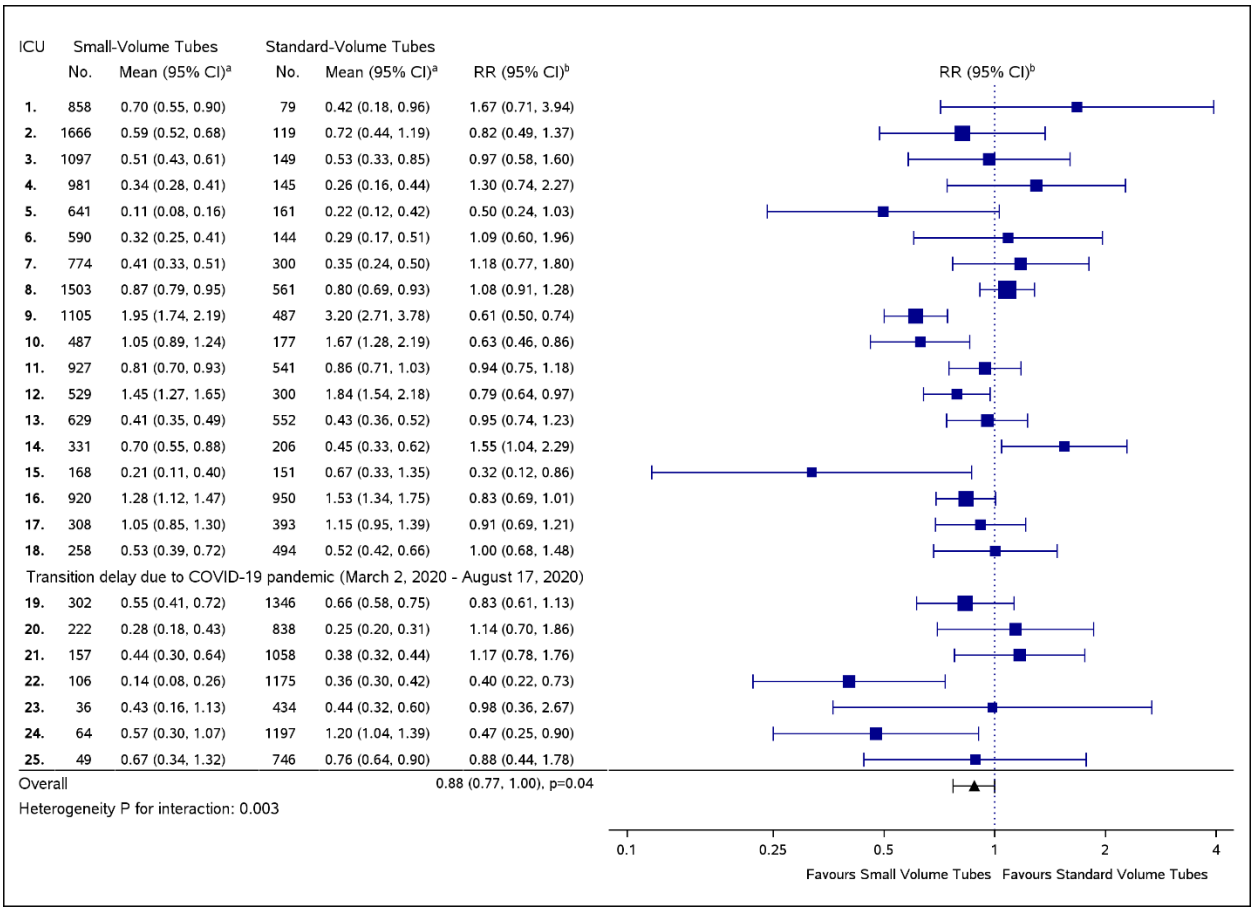
eFigure 2: RBC units per patient per ICU stay before and after transition to small-volume tubes at individual ICUs (secondary analysis population)



CI, confidence interval; ICU, intensive care unit; RR, relative risk.

[a] Mean (95% CI) RBC units per patient per median ICU stay.

[b] Relative risk is adjusted for age and sex.

eFigure 2. Stratified box-and-whisker plot showing the mean (95% confidence interval) number of RBC units per patient per median ICU stay at individual ICUs. Includes patients admitted during the transition delay due to COVID-19 pandemic. The square boxes denote the relative risk of RBC transfusion before and after transition to small-volume tubes adjusted for age and sex. The mean area of the squares is proportional to the corresponding total sample size of the ICU. Each ICU is represented by one row and displayed in the order of transition to small-volume tubes.

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69 **eTable 1: Blood collection tube volumes before and after transition to small-volume tubes at participating ICUs**

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Site	Patients ≥48 hours in ICU	Standard-Volume Tubes / Small-Volume Tubes (mL)						
		EDTA (lavender)	Fluoride (grey)	Lithium heparin (green)	Citrate (light blue)	Serum (red)	Serum separator (gold)	Plasma separator (light green)
A	2064	4.0 / 2.0	Not Used	6.0 / 2.0	1.8 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
B	1870	4.0 / 2.0	6.0 / 2.0	4.0 / 2.0	2.7 / 1.8	5.0 / 3.0	5.0 / 3.5	4.5 / 3.0
C	1785	4.0 / 2.0	4.0 / 2.0	4.0 / 2.0	1.8 / 1.8	9.0 / 2.0	5.0 / 3.5	4.5 / 3.0
D	1648	4.0 / 2.0	4.0 / 2.0	4.0 / 2.0	2.7 / 1.8	4.0 / 2.0	Not Used	Not Used
E	1592	4.0 / 2.0	Not Used	4.0 / 2.0	2.7 / 1.8	4.0 / 2.0	3.5 / 3.5	4.5 / 3.0
F	1468	2.0 / 2.0	6.0 / 2.0	4.0 / 3.0	2.7 / 1.8	6.0 / 3.0	5.0 / 3.5	4.5 / 3.0
G	1281	4.0 / 2.0	Not Used	4.0 / 2.0	2.7 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
H	1261	4.0 / 2.0	4.0 / 2.0	Not Used	2.7 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
I	1246	4.0 / 2.0	4.0 / 2.0	4.0 / 2.0	2.7 / 1.8	4.0 / 2.0	Not Used	Not Used
J	1215	2.0 / 2.0	6.0 / 2.0	4.0 / 2.0	2.7 / 1.8	10.0 / 2.0	5.0 / 3.5	4.5 / 3.0
K	1181	4.0 / 2.0	Not Used	4.0 / 2.0	2.7 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
L	1126	4.0 / 2.0	4.0 / 2.0	2.0 / 2.0	2.7 / 1.8	3.0 / 2.0	3.5 / 3.5	3.0 / 3.0
M	1074	2.0 / 2.0	6.0 / 2.0	4.0 / 2.0	2.7 / 1.8	10.0 / 2.0	5.0 / 3.5	4.5 / 3.0
N	1060	2.0 / 2.0	6.0 / 2.0	4.0 / 2.0	2.7 / 1.8	10.0 / 2.0	5.0 / 3.5	4.5 / 3.0
O	937	3.0 / 2.0	Not Used	4.0 / 2.0	2.7 / 1.8	4.0 / 2.0	3.5 / 3.5	Not Used
P	829	4.0 / 2.0	4.0 / 2.0	Not Used	2.7 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
Q	802	4.0 / 2.0	2.0 / 2.0	4.0 / 2.0	1.8 / 1.8	4.0 / 4.0	3.5 / 3.5	Not Used
R	795	4.0 / 2.0	4.0 / 2.0	Not Used	2.7 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
S	752	3.0 / 2.0	Not Used	4.0 / 2.0	2.7 / 1.8	4.0 / 2.0	5.0 / 3.5	4.5 / 3.0
T	734	3.0 / 2.0	2.5 / 2.0	3.0 / 2.0	2.7 / 1.8	Not Used	5.0 / 3.5	4.5 / 3.0

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Site	Patients ≥48 hours in ICU	Standard-Volume Tubes / Small-Volume Tubes (mL)						
		EDTA (lavender)	Fluoride (grey)	Lithium heparin (green)	Citrate (light blue)	Serum (red)	Serum separator (gold)	Plasma separator (light green)
U	701	4.0 / 2.0	6.0 / 2.0	4.0 / 2.0	2.7 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
V	664	4.0 / 2.0	4.0 / 2.0	Not Used	2.7 / 1.8	6.0 / 2.0	5.0 / 3.5	4.5 / 3.0
W	537	4.0 / 2.0	4.0 / 2.0	4.0 / 2.0	4.5/ 1.8	4.0 / 2.0	Not Used	Not Used
X	470	4.0 / 2.0	2.0 / 2.0	6.0 / 2.0	4.5 / 1.8	10.0 / 2.0	5.0 / 3.5	10.0 / 3.0
Y	319	3.0 / 2.0	2.5 / 2.0	3.0 / 2.0	2.7 / 1.8	Not Used	5.0/ 3.5	4.5 / 3.0

EDTA, ethylenediaminetetraacetic acid.

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73 **eTable 2: Cluster characteristics and baseline characteristics of all patients admitted to ICU ≥48 hours (secondary population)**

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Characteristics	Clusters	
Sites, No.	25	
Province in Canada, No. of sites		
Quebec, Canada	14	
Ontario, Canada	9	
Manitoba, Canada	1	
New Brunswick, Canada	1	
Total cluster size, median (IQR), patients	1074 (752, 1281)	
Cluster-period size, median (IQR), patients	70 (48, 97)	
Characteristics		
Characteristics	**All patients admitted to ICU ≥48 hours (n=27,411)**	
	Small-Volume Tubes (n=14,708)	**Standard-Volume Tubes (n=12,703)**
Age, mean (SD), years	63.3 (15.8)	62.8 (16.1)
Age > 70 years, No. (%)	5448/14708 (37.3)	4652/12703 (37.3)
Sex, No. (%)		
Female	5804/14706 (39.5)	4832/12625 (38.3)
Male	8902/14706 (60.5)	7793/12625 (61.7)
Most responsible diagnosis[a], No. (%)		
Cardiovascular	3329/13138 (25.3)[b]	1813/9659 (18.8)[b]
Nervous System	1586/13138 (12.1)	1365/9659 (14.1)
Other	1469/13138 (11.2)[b]	784/9659 (8.1)[b]
Respiratory	1461/13138 (11.1)	996/9659 (10.3)
Injury	1363/13138 (10.4)[b]	1932/9659 (20.0)[b]
Cancer	1152/13138 (8.8)	890/9659 (9.2)
Infection	1134/13138 (8.6)	743/9659 (7.7)
Digestive	1106/13138 (8.4)	814/9659 (8.4)
Genitourinary	299/13138 (2.3)	209/9659 (2.2)
Endocrine	239/13138 (1.8)	113/9659 (1.2)

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Characteristics	All patients admitted to ICU ≥48 hours (n=27,411)	
	Small-Volume Tubes (n=14,708)	Standard-Volume Tubes (n=12,703)
Initial hemoglobin concentration (female)[c], g/dL		
mean (SD)	10.45 (2.11)	10.64 (2.05)
median (IQR)	10.40 (8.90, 11.90)	10.70 (9.20, 12.10)
Initial hemoglobin concentration (male)[c], g/dL		
mean (SD)	11.16 (2.44)	11.27 (2.33)
median (IQR)	11.20 (9.30, 12.90)	11.30 (9.50, 12.90)
Initial hemoglobin (female)[c], g/dL		
<7.0, No. (%)	186/5431 (3.4)	132/4560 (2.9)
7.0-9.0, No. (%)	1216/5431 (22.4)	863/4560 (18.9)
9.0-11.0, No. (%)	1875/5431 (34.5)	1536/4560 (33.7)
11.0-13.0, No. (%)	1545/5431 (28.4)	1487/4560 (32.6)
>13.0, No. (%)	609/5431 (11.2)	542/4560 (11.9)
Initial hemoglobin (male)[c], g/dL		
<7.0, No. (%)	273/8380 (3.3)	171/7384 (2.3)
7.0-9.0, No. (%)	1434/8380 (17.1)	1137/7384 (15.4)
9.0-11.0, No. (%)	2234/8380 (26.7)	1983/7384 (26.9)
11.0-13.0, No. (%)	2489/8380 (29.7)	2346/7384 (31.8)
>13.0, No. (%)	1950/8380 (23.3)	1747/7384 (23.7)
Creatinine[c], mg/dL		
mean (SD)	1.53 (1.50)[b]	1.37 (1.33)[b]
median (IQR)	1.00 (0.75, 1.57)	0.94 (0.71, 1.38)
Creatinine[c], mg/dL		
<1.5, No. (%)	9508/13018 (73.0)	9223/11850 (77.8)
1.5-3.0, No. (%)	2156/13018 (16.6)	1671/11850 (14.1)
>3.0, No. (%)	1354/13018 (10.4)	956/11850 (8.1)

ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

[a] ICD codes. Data was provided by 20/25 participating ICUs.

[b] Standardized difference >0.1.

[c] Hemoglobin and creatinine data was provided by 24/25 participating ICUs.

SI conversion factors: To convert hemoglobin to g/L, multiply values by 10. To convert creatinine to umol/L, multiply values by 88.4.

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eTable 3. Baseline characteristics of patients admitted during the pandemic-related delay and other study periods

	Patients admitted during pandemic-related delay in transitions[a]	Patients admitted during other study periods
Total, n	6,210	21,201
Age, years Mean (SD)	62.5 (15.9)	63.2 (16.0)
Female Sex, n (%)	2368 (38.4)	8268 (39.1)
Most responsible diagnosis[b]		
Cardiovascular	1135 (21.8)	4007 (22.8)
Nervous system	640 (12.3)	2311 (13.1)
Respiratory	529 (10.2)	1928 (11.0)
Injury	753 (14.5)	2542 (14.4)
Infection	394 (7.6)	1483 (8.4)
Cancer	462 (8.9)	1580 (9.0)
Digestive	405 (7.8)	1515 (8.6)
Genitourinary	101 (1.9)	407 (2.3)
Endocrine	85 (1.6)	267 (1.5)
Other	700 (13.5) [c]	1553 (8.8) [c]
Hemoglobin concentration (female), g/dL		
Mean (SD)	10.55 (2.12)	10.53 (2.07)
Median (IQR)	10.50 (9.00, 12.00)	10.50 (9.00, 12.00)
Hemoglobin concentration (male), g/dL		
Mean (SD)	11.40 (2.41)	11.16 (2.38)
Median (IQR)	11.50 (9.60, 13.20)	11.20 (9.40, 12.90)
Initial hemoglobin <7.0 g/dL, n (%)	165 (2.8)	598 (3.0)
Creatinine, mg/dL		
Mean (SD)	1.44 (1.43)	1.46 (1.42)
Median (IQR)	0.95 (0.72, 1.45)	0.97 (0.74, 1.50)

ICU, intensive care unit; IQR, interquartile range; SD, standard deviation.

[a]Pandemic period lasted from March 2, 2021 to August 17, 2021 at all sites.

[b]ICD codes. Denominator: 22,797 – all patients admitted before and after transition, 5,204 – patients admitted during pandemic.

[c]Standardized difference >0.1 between patients admitted during pandemic-related transition delay and other study periods.

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eTable 4. Selected baseline characteristics in individual ICUs

Site	Baseline characteristics							
	Age, mean (SD), years		Sex – Female, No. (%)		Initial hemoglobin (female), median (IQR), g/dL, 24/25 sites		Initial hemoglobin (male), median (IQR), g/dL, 24/25 sites	
	Small-Volume Tubes	Standard-Volume Tubes	Small-Volume Tubes	Standard-Volume Tubes	Small-Volume Tubes	Standard-Volume Tubes	Small-Volume Tubes	Standard-Volume Tubes
1.	65.0 (15.2)	68.6 (12.5)	265/640 (41.1)	30/79 (38.0)	10.6 (9.0, 11.8)	10.4 (9.4, 11.6)	11.5 (9.7, 12.8)	11.0 (9.7, 12.2)
2.	57.1 (16.5)	57.8 (16.0)	506/1278 (40.0)	53/119 (45.0)	10.1 (8.4, 11.6)	10.1 (8.6, 12.1)	11.1 (9.0, 13.2)	10.8 (8.7, 13.3)
3.	64.9 (16.1)	66.8 (14.6)	398/826 (48.2)	70/149 (47.0)	9.7 (8.2, 11.2)	9.8 (7.9, 10.9)	10.0 (8.4, 12.0)	10.4 (9.0, 12.1)
4.	69.9 (16.0)	70.2 (17.5)	324/748 (43.3)	65/145 (44.8)	10.7 (9.3, 12.3)	10.3 (8.0, 11.6)	11.7 (9.7, 13.3)	11.4 (9.4, 13.0)
5.	64.3 (16.1)	61.4 (17.4)	187/448 (41.7)	76/161 (47.2)	10.7 (9.1, 12.1)	10.5 (9.0, 12.2)	11.1 (9.0, 12.9)	10.7 (9.0, 12.3)
6.	61.1 (17.9)	63.5 (18.9)	171/443 (38.6)	53/144 (36.8)	11.0 (9.3, 12.3)	11.2 (10.1, 12.3)	12.1 (9.5, 13.8)	11.4 (9.1, 13.7)
7.	65.4 (15.3)	65.7 (13.8)	236/554 (42.6)	110/300 (36.7)	11.1 (9.5, 12.4)	11.1 (9.2, 12.2)	12.1 (9.8, 13.6)	11.6 (9.4, 13.6)
8.	66.1 (12.3)	66.3 (12.6)	355/1011 (35.1)	201/560 (36.0)	10.1 (9.1, 11.1)	10.4 (9.3, 11.5)	10.7 (9.3, 12.2)	10.8 (9.6, 12.1)
9.	64.8 (14.9)	66.5 (14.3)	244/696 (35.1)	172/487 (35.3)	10.5 (9.2, 11.9)	9.8 (8.8, 11.6)	10.5 (9.0, 12.0)	10.4 (8.9, 11.8)
10.	59.7 (14.7)	60.0 (13.7)	125/329 (38.0)	66/177 (37.3)	10.0 (8.5, 11.4)	10.0 (8.6, 11.6)	10.5 (8.7, 12.8)	9.9 (8.6, 12.4)
11.	61.1 (17.5)	59.4 (17.8)	248/598 (41.5)	205/541 (37.9)	10.5 (8.8, 12.2)	10.8 (9.2, 12.3)	11.3 (9.4, 13.1)	11.1 (9.3, 12.8)
12.	67.1 (12.0)	66.7 (11.1)	99/313 (31.6)	96/300 (32.0)	10.1 (8.7, 11.3)	10.0 (8.9, 11.2)	10.1 (9.0, 11.1)	10.1 (9.0, 11.5)
13.	62.8 (13.7)	64.9 (13.1)	173/385 (44.9)	212/552 (38.4)	10.2 (8.6, 11.8)	9.6 (8.5, 11.4)	10.9 (9.1, 12.8)	10.7 (9.2, 12.7)
14.	62.2 (17.3)	63.8 (17.6)	79/198 (39.9)	94/206 (45.6)	10.5 (8.3, 11.7)	10.1 (8.9, 11.9)	10.0 (7.8, 11.9)	10.6 (8.4, 12.3)
15.	67.0 (16.2)	63.5 (17.5)	25/78 (32.1)	55/151 (36.4)	11.6 (10.5, 13.1)	11.0 (9.6, 12.6)	12.7 (10.8, 14.2)	12.5 (10.1, 13.7)
16.	64.5 (15.2)	65.0 (15.0)	198/524 (37.8)	362/950 (38.1)	10.2 (8.7, 12.1)	9.7 (8.5, 11.6)	11.2 (9.2, 12.9)	10.6 (8.8, 12.6)
17.	61.8 (15.0)	63.8 (15.0)	64/150 (42.7)	146/393 (37.2)	10.8 (9.2, 12.1)	10.7 (9.5, 12.4)	11.2(9.5, 13.0)	11.3 (9.5, 12.9)
18.	64.0 (15.3)	64.6 (15.2)	39/105 (37.1)	197/494 (39.9)	N/A	N/A	N/A	N/A
19.	59.4 (18.1)	59.8 (17.9)	104/302 (34.4)	386/978 (39.5)	10.7 (9.5, 12.0)	10.8 (9.2, 12.3)	11.9 (10.0, 13.3)	11.2 (9.4, 12.9)
20.	65.4 (14.3)	65.9 (15.4)	103/222 (46.4)	266/603 (44.1)	11.1 (9.2, 12.8)	11.2 (9.8, 12.5)	12.3 (10.5, 13.4)	11.8 (10.1, 13.3)
21.	64.4 (14.1)	65.0 (14.2)	52/157 (33.1)	257/785 (32.7)	10.5 (9.5, 11.3)	10.5 (9.6, 11.7)	11.7 (10.0, 13.0)	11.7 (10.4, 12.9)
22.	59.8 (15.8)	57.6 (17.5)	44/106 (41.5)	349/931 (37.5)	11.0 (10.3, 12.1)	10.9 (9.5, 12.0)	11.7 (10.8, 13.3)	11.9 (10.3, 13.2)
23.	63.7 (13.7)	64.2 (14.8)	12/36 (33.3)	102/298 (34.2)	10.9 (9.2, 13.1)	10.5 (8.7, 12.1)	11.3 (8.9, 13.7)	11.2 (9.5, 12.7)
24.	59.6 (19.8)	61.7 (18.8)	19/64 (29.7)	284/863 (32.9)	10.7 (9.4, 12.5)	10.8 (9.5, 12.4)	12.0 (9.3, 13.4)	11.8 (10.4, 13.2)
25.	58.7 (14.2)	58.8 (14.6)	20/49 (40.8)	271/545 (49.7)	10.7 (9.3, 11.5)	11.2 (9.9,12.4)	11.4 (9.7, 12.6)	11.6 (9.7, 13.4)

IQR, interquartile range; N/A, not available; SD, standard deviation

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92 **eTable 5: Study outcomes of all patients admitted to ICU ≥48 hours (secondary population)**

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Outcome		All patients admitted ≥48 hrs[a], n=27,411			
		Small-Volume Tubes, n=14,708	Standard-Volume Tubes, n=12,703	RR[b] (95% CI)	MD[b] (95% CI)
Primary outcome					
RBC units transfused in ICU per patient per median ICU stay	LSM (95% CI)	0.71 (0.53, 0.93)	0.80 (0.61, 1.06)	0.88 (0.77, 1.00), p=0.04[c]	-0.10 (-0.21, -0.002)
	Crude mean (SD)	0.78 (2.20)	0.84 (2.67)		
Secondary outcomes					
Specimens with insufficient quantity for analysis[d e]	No. (%)	65 (0.023)	64 (0.028)		-0.006 (-0.02, 0.003)[f]
Patients received ≥ 1 units RBC transfusion in ICU	No. (%)	4296 (29.2)	3840 (30.2)	0.97 (0.90, 1.04)	-1.02 (-3.17, 0.98)[f]
Change in hemoglobin from ICU admission to ICU discharge adjusted for RBC transfusions[g h i], g/dL	Median (IQR)	-1.40 (-3.10, -0.30)	-1.50 (-3.20, -0.40)		0.17 (0.05, 0.29)
Duration of ICU admission, days	Median (IQR)	4.0 (3.0, 8.0)	4.0 (3.0, 7.0)	0.97 (0.93, 1.01)	-0.21 (-0.47, 0.05)
Duration of hospital admission, days	Median (IQR)	11.0 (7.0, 20.0)	11.0 (7.0, 19.0)	1.00 (0.98, 1.03)	0.05 (-0.31, 0.40)
Mortality in ICU	No. (%)	2094 (14.2)	1493 (11.8)	0.98 (0.88, 1.09)[j]	-0.31 (-1.92, 1.13)[f]
Mortality in hospital	No. (%)	2538 (17.3)	1887 (14.9)	0.99 (0.90, 1.09)[j]	-0.18 (-1.87, 1.35)[f]

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Outcome		All patients[a], n=27,411			
		Small-Volume Tubes, n=14,708	Standard-Volume Tubes, n=12,703	RR[b] (95% CI)	MD[b] (95% CI)
Post-hoc exploratory outcomes					
Hemoglobin within 48hrs of ICU discharge[g i], g/dL	Median (IQR)	9.50 (8.30, 11.20)	9.60 (8.40, 11.20)	1.01 (1.00, 1.02)	0.11 (0.03, 0.19)
Change in hemoglobin from ICU admission to ICU discharge[g i], g/dL	Median (IQR)	-0.80 (-2.00, 0.20)	-0.90 (-2.10, 0.10)		0.12 (0.05, 0.19)
Change in hemoglobin from ICU admission to ICU discharge in patients without RBC transfusions[g k], g/dL	Median (IQR)	-0.90 (-2.00, 0.00)	-1.00 (-2.10, 0.00)		0.10 (0.02, 0.18)

CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LSM, least squares mean; MD, mean difference; RBC, red blood cell; RR, relative risk; SD, standard deviation.

[a] Patients admitted during pandemic-related delay in transitions to small-volume tubes (March 2, 2020 - August 17, 2020) were included.

[b] Relative Risk and Mean Difference results were adjusted for age and sex and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[c] P value represents the result of the hypothesis test for the significance of the intervention (transition to small-volume tubes) effect and was calculated by generalized linear mixed model adjusted for age and sex and accounted for the stepped wedge design.

[d] Number of tubes with insufficient quantity for analysis per total number of specimens sent for hemoglobin (ethylenediaminetetraacetic acid [EDTA] tubes) and creatinine (lithium or sodium heparin tubes) tests during ICU admission; analyzed using Chi-Square test of equality of two proportions.

[e] Denominators for the small-volume tube group vs. standard-volume tube group were 285273 vs. 224868, respectively.

[f] Percent difference in % was presented for binary outcomes and was adjusted for age and sex and accounted for the stepped wedge design. Absolute percent difference in % without any adjustment was presented for specimens with insufficient quantity outcome.

[g] Analyses were adjusted for baseline admission hemoglobin in addition to adjusting for age and sex.

[h] Hemoglobin adjusted for RBC transfusion 1 transfusion = Hb – 1 g/dL. Values <0 were substituted with 0 (3.7% of values).

[i] Denominators for the small-volume tube group vs. standard-volume tube group were 13170 vs. 11457, respectively.

[j] Unadjusted RR (95% CI) for Mortality in ICU and Mortality in hospital were 1.21 (1.14, 1.29) and 1.16 (1.10, 1.23), respectively.

[k] Denominators for the small-volume tube group vs. standard-volume tube group were 9052 vs. 7851, respectively.

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eTable 6: Study outcomes among patients with any duration of ICU admission (excluding patients admitted during pandemic-related delay)

Outcome		Population with any duration of ICU admission excluding patients admitted during pandemic-delay[a], n=38,882			
		Small-Volume Tubes, n=18,616	Standard-Volume Tubes, n=20,266	RR[b] (95% CI)	MD[b] (95% CI)
Primary outcome					
RBC units transfused in ICU per patient per 4 days in ICU (median in primary analysis)	LSM (95% CI)	0.77 (0.56, 1.07)	0.80 (0.58, 1.10)	0.97 (0.83, 1.14), p=0.72[c]	-0.02 (-0.16, 0.10)
	Crude mean (SD)	0.86 (4.00)	0.87 (4.10)		
Secondary outcomes					
Specimens with insufficient quantity for analysis[d e]	No. (%)	50 (0.022)	80 (0.035)		-0.13 (-0.24, -0.01)[f]
Patients received ≥ 1 units RBC transfusion in ICU	No. (%)	3753 (20.2)	4204 (20.7)	0.98 (0.91, 1.05)	-0.51 (-2.07, 0.94)[f]
Change in hemoglobin from ICU admission to ICU discharge adjusted for RBC transfusions[g h i], g/dL	Median (IQR)	-0.80 (-2.20, 0.00)	-0.90 (-2.30, 0.00)		0.11 (0.02, 0.20)
Duration of ICU admission, days	Median (IQR)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	0.96 (0.92, 1.00)	-0.18 (-0.37, -0.001)
Duration of hospital admission, days	Median (IQR)	7.0 (5.0, 13.0)	7.0 (5.0, 12.0)	1.02 (0.99, 1.05)	0.20 (-0.08, 0.48)
Mortality in ICU	No. (%)	2483 (13.3)	2220 (11.0)	0.96 (0.88, 1.05)[j]	-0.58 (-1.92, 0.65)[f]
Mortality in hospital	No. (%)	2915 (15.7)	2696 (13.3)	0.96 (0.89, 1.04)[j]	-0.66 (-2.06, 0.63)[f]

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Outcome		Population with any duration of ICU admission excluding patients admitted during pandemic-related delay [a], n=38,882			
		Small-Volume Tubes, n=18,616	Standard-Volume Tubes, n=20,266	RR[b] (95% CI)	MD[b] (95% CI)
Post-hoc exploratory outcomes					
Hemoglobin within 48hrs of ICU discharge[g i], g/dL	Median (IQR)	10.00 (8.60, 11.70)	10.00 (8.60, 11.60)	1.01 (1.00, 1.01)	0.08 (0.01, 0.14)
Change in hemoglobin from ICU admission to ICU discharge[g i], g/dL	Median (IQR)	-0.50 (-1.50, 0.00)	-0.60 (-1.60, 0.00)		0.08 (0.02, 0.13)
Change in hemoglobin from ICU admission to ICU discharge in patients without RBC transfusions[g k], g/dL	Median (IQR)	-0.50 (-1.40, 0.00)	-0.60 (-1.50, 0.00)		0.06 (0.01, 0.12)

CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LSM, least squares mean; MD, mean difference; RBC, red blood cell; RR, relative risk; SD, standard deviation.

[a] Patients admitted during pandemic-related delay in transitions to small-volume tubes (March 2, 2020 - August 17, 2020) were excluded.

[b] Relative Risk and Mean Difference were adjusted for age and sex and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[c] P value represents the result of the hypothesis test for the significance of the intervention (transition to small-volume tubes) effect and was calculated by generalized linear mixed model adjusted for age and sex and accounted for the stepped wedge design.

[d] Number of tubes with insufficient quantity for analysis per total number of specimens sent for hemoglobin (ethylenediaminetetraacetic acid [EDTA] tubes) and creatinine (lithium or sodium heparin tubes) tests during ICU admission; analyzed using Chi-Square test of equality of two proportions.

[e] Denominators for the small-volume tube group vs. standard-volume tube group were 231223 vs. 231451, respectively.

[f] Percent difference in % was presented for binary outcomes and was adjusted for age and sex and accounted for the stepped wedge design. Absolute percent difference in % without any adjustment was presented for specimens with insufficient quantity outcome.

[g] Analyses were adjusted for baseline admission hemoglobin in addition to adjusting for age and sex.

[h] Hemoglobin adjusted for RBC transfusion 1 transfusion = Hb – 1 g/dL. Values <0 were substituted with 0 (<5% of values).

[i] Denominators for the small-volume tube group vs. standard-volume tube group were 16412 vs. 17313, respectively.

[j] Unadjusted RR (95% CI) for Mortality in ICU and Mortality in hospital were 1.22 (1.15, 1.28) and 1.18 (1.12, 1.24), respectively.

[k] Denominators for the small-volume tube group vs. standard-volume tube group were 12806 vs. 13400, respectively.

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eTable 7: Study outcomes among patients with any duration of ICU admission (including patients admitted during pandemic-related delay)

Outcome		Population with any duration of ICU admission[a], n=50,485			
		Small-Volume Tubes, n=27,294	Standard-Volume Tubes, n=23,191	RR[b] (95% CI)	MD[b] (95% CI)
Primary outcome					
RBC units transfused in ICU per patient per 4 days in ICU (median in primary analysis)	LSM (95% CI)	0.76 (0.56, 1.02)	0.80 (0.60, 1.08)	0.94 (0.82, 1.09), p=0.43[c]	-0.05 (-0.17, 0.06)
	Crude mean (SD)	0.84 (3.83)	0.83 (3.99)		
Secondary outcomes					
Specimens with insufficient quantity for analysis[d e]	No. (%)	90 (0.026)	84 (0.032)		-0.03 (-0.14, 0.07)[f]
Patients received ≥ 1 units RBC transfusion in ICU	No. (%)	5471 (20.0)	4717 (20.3)	0.95 (0.89, 1.02)	-0.99 (-2.40, 0.32)[f]
Change in hemoglobin from ICU admission to ICU discharge adjusted for RBC transfusions[g h i], g/dL	Median (IQR)	-0.90 (-2.20, 0.00)	-0.90 (-2.30, 0.00)		0.13 (0.05, 0.21)
Duration of ICU admission, days	Median (IQR)	2.0 (1.0, 5.0)	2.0 (1.0, 5.0)	0.96 (0.93, 1.00)	-0.17 (-0.34, -0.01)
Duration of hospital admission, days	Median (IQR)	7.0 (5.0, 13.0)	7.0 (5.0, 13.0)	1.00 (0.97, 1.02)	-0.02 (-0.28, 0.23)
Mortality in ICU	No. (%)	3532 (12.9)	2560 (11.0)	0.96 (0.89, 1.04)[j]	-0.59 (-1.78, 0.51)[f]
Mortality in hospital	No. (%)	4163 (15.3)	3139 (13.5)	0.95 (0.89, 1.02)[j]	-0.78 (-2.02, 0.38)[f]

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Outcome		Population with any duration of ICU admission[a], n=50,485			
		Small-Volume Tubes, n=27,294	Standard-Volume Tubes, n=23,191	RR[b] (95% CI)	MD[b] (95% CI)
Post-hoc exploratory outcomes					
Hemoglobin within 48hrs of ICU discharge[g i], g/dL	Median (IQR)	10.00 (8.60, 11.70)	10.00 (8.60, 11.70)	1.01 (1.00, 1.01)	0.08 (0.02, 0.14)
Change in hemoglobin from ICU admission to ICU discharge[g i], g/dL	Median (IQR)	-0.50 (-1.50, 0.00)	-0.60 (-1.60, 0.00)		0.08 (0.02, 0.13)
Change in hemoglobin from ICU admission to ICU discharge in patients without RBC transfusions[g k], g/dL	Median (IQR)	-0.50 (-1.40, 0.00)	-0.60 (-1.50, 0.00)		0.05 (-0.003, 0.10)

CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LSM, least squares mean; MD, mean difference; RBC, red blood cell; RR, relative risk; SD, standard deviation.

[a] Patients admitted during pandemic-related delay in transitions to small-volume tubes (March 2, 2020 - August 17, 2020) were included.

[b] Relative Risk and Mean Difference were adjusted for age and sex and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[c] P value represents the result of the hypothesis test for the significance of the intervention (transition to small-volume tubes) effect and was calculated by generalized linear mixed model adjusted for age and sex and accounted for the stepped wedge design.

[d] Number of tubes with insufficient quantity for analysis per total number of specimens sent for hemoglobin (ethylenediaminetetraacetic acid [EDTA] tubes) and creatinine (lithium or sodium heparin tubes) tests during ICU admission; analyzed using Chi-Square test of equality of two proportions.

[e] Denominators for the small-volume tube group vs. standard-volume tube group were 343458 vs. 263595, respectively.

[f] Percent difference in % was presented for binary outcomes and was adjusted for age and sex and accounted for the stepped wedge design. Absolute percent difference in % without any adjustment was presented for specimens with insufficient quantity outcome.

[g] Analyses were adjusted for baseline admission hemoglobin in addition to adjusting for age and sex.

[h] Hemoglobin adjusted for RBC transfusion 1 transfusion = Hb – 1 g/dL. Values <0 were substituted with 0 (<5% of values).

[i] Denominators for the small-volume tube group vs. standard-volume tube group were 23726 vs. 19900, respectively.

[j] Unadjusted RR (95% CI) for Mortality in ICU and Mortality in hospital were 1.17 (1.12, 1.23) and 1.13 (1.08, 1.18), respectively.

[k] Denominators for the small-volume tube group vs. standard-volume tube group were 18520 vs. 15500, respectively.

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eTable 8: Subgroup analyses for the effect of transition to small-volume tubes on RBC units transfused in ICU (primary population)

Outcome	Primary population[a], n=21,201							
	Subgroup	No. (%) of patients	Small-Volume Tubes, n=10,261 LSM (95% CI)	Standard-Volume Tubes, n=10,940 LSM (95% CI)	RR[b] (95% CI)	MD[b] (95% CI)	P	P for interaction
Primary outcome								
RBC units transfused in ICU per patient per median ICU stay	Overall	21201	0.72 (0.52, 0.98)[c]	0.79 (0.58, 1.07)[c]	0.91 (0.79, 1.05)	-0.07 (-0.19, 0.03)	0.19[d]	
	Age, years	21201						0.91[e]
	≤65	10218 (48.2)	0.75 (0.55, 1.02)[f]	0.81 (0.60, 1.10)[f]	0.93 (0.76, 1.13)	-0.06 (-0.24, 0.09)	0.46[d]	
	>65	10983 (51.8)	0.68 (0.49, 0.94)[g]	0.76 (0.55, 1.06)[g]	0.89 (0.72, 1.09)	-0.09 (-0.26, 0.05)	0.25[d]	
	Sex	21171						0.09[e]
	Female	8268 (39.1)	0.72 (0.52, 1.00)[h]	0.68 (0.49, 0.94)[h]	1.06 (0.86, 1.31)	0.04 (-0.12, 0.17)	0.61[d]	
	Male	12903 (61.0)	0.74 (0.54, 1.01)[i]	0.88 (0.64, 1.20)[i]	0.84 (0.69, 1.01)	-0.14 (-0.33, 0.01)	0.06[d]	
	Initial hemoglobin, g/dL	19981						0.19[e]
	≤10.9	10255 (51.3)	1.15 (0.90, 1.49)[j]	1.26 (0.98, 1.62)[j]	0.92 (0.78, 1.07)	-0.11 (-0.32, 0.08)	0.27[d]	
	>10.9	9726 (48.7)	0.27 (0.16, 0.43)[k]	0.33 (0.20, 0.53)[k]	0.81 (0.59, 1.12)	-0.06 (-0.18, 0.03)	0.21[d]	

CI, confidence interval; ICU, intensive care unit; LSM, least squares mean; MD, mean difference; RBC, red blood cell; RR, relative risk.

[a] Patients admitted during pandemic-related delay in transitions to small-volume tubes (March 2, 2020 - August 17, 2020) were excluded.

[b] Relative Risk/Mean Difference results were adjusted for age and sex (if not a subgroup analysis by sex) and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[c] Denominators for the small-volume tube group vs. standard-volume tube group are 10260 vs. 10911, respectively.

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[d] P value represents the result of the hypothesis test for the significance of the intervention (transition to small-volume tubes) effect and was calculated by generalized linear mixed model adjusted for age and sex (if not a subgroup analysis by sex) and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[e] P value represents the result of the hypothesis test for the significance of the interaction between intervention (transition to small-volume tubes) and subgroup allocation and was calculated by generalized linear mixed model adjusted for age and sex (if not a subgroup analysis by sex) and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[f] Denominators for the small-volume tube group vs. standard-volume tube group are 4920 vs. 5282, respectively.

[g] Denominators for the small-volume tube group vs. standard-volume tube group are 5340 vs. 5629, respectively.

[h] Denominators for the small-volume tube group vs. standard-volume tube group are 4090 vs. 4178, respectively.

[i] Denominators for the small-volume tube group vs. standard-volume tube group are 6170 vs. 6733, respectively.

[j] Denominators for the small-volume tube group vs. standard-volume tube group are 5111 vs. 5129, respectively.

[k] Denominators for the small-volume tube group vs. standard-volume tube group are 4594 vs. 5118, respectively.

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eTable 9: Subgroup analysis for the effect of intervention on RBC units transfused on ICU (secondary population)

Outcome	Secondary population[a], n=27,411							
	Subgroup	No. (%) of patients	Small-Volume Tubes, n=14,708 LSM (95% CI)	Standard-Volume Tubes, n=12,703 LSM (95% CI)	RR[b] (95% CI)	MD[b] (95% CI)	P	P for interaction
Primary outcome								
RBC units transfused in ICU per patient per median ICU stay	Overall	27411	0.71 (0.53, 0.93)[c]	0.80 (0.61, 1.06)[c]	0.88 (0.77, 1.00)	-0.10 (-0.21, -0.002)	0.04[d]	
	Age, years	27411						0.49[e]
	≤65	13368 (48.8)	0.73 (0.56, 0.97)[f]	0.83 (0.63, 1.09)[f]	0.89 (0.75, 1.06)	-0.09 (-0.25, 0.04)	0.19[d]	
	>65	14043 (51.2)	0.68 (0.50, 0.91)[g]	0.77 (0.58, 1.04)[g]	0.87 (0.73, 1.05)	-0.10 (-0.25, 0.03)	0.14[d]	
	Sex	27331						0.09[e]
	Female	10636 (38.9)	0.71 (0.53, 0.94)[h]	0.73 (0.55, 0.96)[h]	0.97 (0.81, 1.17)	-0.02 (-0.17, 0.10)	0.76[d]	
	Male	16695 (61.1)	0.72 (0.54, 0.97)[i]	0.86 (0.65, 1.15)[i]	0.84 (0.71, 0.99)	-0.14 (-0.29, -0.004)	0.04[d]	
	Initial hemoglobin, g/dL	25831						0.03[e]
	≤10.9	13073 (50.6)	1.15 (0.92, 1.45)[j]	1.27 (1.01, 1.60)[j]	0.91 (0.79, 1.04)	-0.12 (-0.31, 0.05)	0.17[d]	
	>10.9	12758 (49.4)	0.26 (0.17, 0.40)[k]	0.34 (0.22, 0.52)[k]	0.77 (0.58, 1.03)	-0.08 (-0.19, 0.01)	0.08[d]	

CI, confidence interval; ICU, intensive care unit; LSM, least squares mean; MD, mean difference; RBC, red blood cell; RR, relative risk.

[a] Patients admitted during pandemic-related delay in transitions to small-volume tubes (March 2, 2020 - August 17, 2020) were included.

[b] Relative Risk/Mean Difference results were adjusted for age and sex (if not a subgroup analysis by sex) and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[c] Denominators for the small-volume tube group vs. standard-volume tube group are 14706 vs. 12625, respectively.

[d] P value represents the result of the hypothesis test for the significance of the intervention (transition to small-volume tubes) effect and was calculated by generalized linear mixed model adjusted for age and sex (if not a subgroup analysis by sex) and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

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[e] P value represents the result of the hypothesis test for the significance of the interaction between intervention (transition to small-volume tubes) and subgroup allocation and was calculated by generalized linear mixed model adjusted for age and sex (if not a subgroup analysis by sex) and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[f] Denominators for the small-volume tube group vs. standard-volume tube group are 7116 vs. 6208, respectively.

[g] Denominators for the small-volume tube group vs. standard-volume tube group are 7590 vs. 6417, respectively.

[h] Denominators for the small-volume tube group vs. standard-volume tube group are 5804 vs. 4832, respectively.

[i] Denominators for the small-volume tube group vs. standard-volume tube group are 8902 vs. 7793, respectively.

[j] Denominators for the small-volume tube group vs. standard-volume tube group are 7218 vs. 5822, respectively.

[k] Denominators for the small-volume tube group vs. standard-volume tube group are 6593 vs. 6122, respectively.

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eTable 10: Sensitivity analysis of primary outcome adjusted for imbalanced baseline characteristics (primary population)

Outcome		Primary population with imbalanced baseline characteristics available[a], n=15,725				
		Small-Volume Tubes, n=7,912	Standard-Volume Tubes, n=7,813	RR[b] (95% CI)	MD[b] (95% CI)	P
Primary outcome						
RBC units transfused in ICU per patient per median ICU stay, adjusted for age and sex only	LSM (95% CI)	0.79 (0.56, 1.10)[c]	0.92 (0.65, 1.29)[c]	0.86 (0.73, 1.01)	-0.13 (-0.29, 0.004)	0.06[d]
	Crude mean (SD)	0.85 (2.35)	1.05 (3.14)			
RBC units transfused in ICU per patient per median ICU stay, adjusted for age, sex, and imbalanced baseline characteristics[a]	LSM (95% CI)	0.83 (0.59, 1.17)[c]	0.96 (0.68, 1.36)[c]	0.86 (0.74, 1.01)	-0.13 (-0.30, 0.01)	0.07[d]
	Crude mean (SD)	0.85 (2.35)	1.05 (3.14)			

CI, confidence interval; ICU, intensive care unit; LSM, least squares mean; MD, mean difference; RBC, red blood cell; RR, relative risk; SD, standard deviation.

[a] Patients admitted during pandemic-related delay in transitions to small-volume tubes (March 2, 2020 - August 17, 2020) were excluded. Data was provided by 19/25 sites. Baseline characteristics with standardized difference >0.1 between patients in small-volume and standard-volume groups were considered imbalanced. For primary population, this variable is injury diagnosis only.

[b] Relative Risk/Mean Difference results were adjusted for age and sex and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[c] Denominators for the small-volume tube group vs. standard-volume tube group are 7912 vs. 7813, respectively.

[d] P value represents the result of the hypothesis test for the significance of the intervention (transition to small-volume tubes) effect and was calculated by generalized linear mixed model adjusted for age and sex and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

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eTable 11: Sensitivity analysis of primary outcome without adjusting for age and sex, and primary outcome model with time-decay correlation

Analysis	RBC units transfused in ICU per patient per median ICU stay	Primary population[a], n=21,201				
		Small-Volume Tubes, n=10,261	Standard-Volume Tubes, n=10,940	RR[b] (95% CI)	MD[b] (95% CI)	P
Adjustment for age and sex (a priori)	LSM (95% CI)	0.72 (0.52, 0.98)[c]	0.79 (0.58, 1.07)[c]	0.91 (0.79, 1.05)	-0.07 (-0.19, 0.03)	0.19[d]
	Crude mean (SD)	0.78 (2.23)	0.88 (2.79)			
No adjustment for age and sex	LSM (95% CI)	0.73 (0.53, 0.99)[e]	0.80 (0.59, 1.09)[e]	0.90 (0.78, 1.04)	-0.08 (-0.20, 0.03)	0.17[d]
	Crude mean (SD)	0.78 (2.23)	0.88 (2.79)			
Analysis with time-decay correlation structure[f]	LSM (95% CI)	0.72 (0.52, 0.98)[c]	0.79 (0.58, 1.07)[c]	0.91 (0.79, 1.05)	-0.07 (-0.19, 0.03)	0.19[d]
	Crude mean (SD)	0.78 (2.23)	0.88 (2.79)			

CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; LSM, least squares mean; MD, mean difference; RBC, red blood cell; RR, relative risk; SD, standard deviation.

[a] Patients admitted during pandemic-related delay in transitions to small-volume tubes (March 2, 2020 - August 17, 2020) were excluded.

[b] Relative Risk/Mean Difference results were accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[c] Denominators for the small-volume tube group vs. standard-volume tube group are 10260 vs. 10911, respectively.

[d] P value represents the result of the hypothesis test for the significance of the intervention (transition to small-volume tubes) effect and was calculated by generalized linear mixed model adjusted for age and sex and accounted for the stepped wedge design with periods modelled as fixed effects, ICU units as a random effect, and length of ICU stay as an offset.

[e] Denominators for the small-volume tube group vs. standard-volume tube group are 10261 vs. 10940, respectively.

[F] To examine the issue of potential correlation misspecification, we conducted a post-hoc analysis using time-decay correlation structure. The observed cluster autocorrelation (CAC) was 0.95 close to 1 used in the power calculation.

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eTable 12: Analysis of primary outcome using pre-specified generalized linear mixed model (GLMM) and post-hoc generalised estimating equation model (GEE)

RBC units transfused in ICU per patient per median ICU stay	RR (95% CI)	MD (95% CI)	P-value
GLMM Model	0.91 (0.79, 1.05)	-0.07 (-0.19, 0.03)	0.19
GEE Model	0.91 (0.60, 1.37)	-0.08 (-0.51, 0.21)	0.63

CI, confidence interval; GEE, generalized estimating equation; GLMM, generalised linear mixed model; ICU, intensive care unit; MD, mean difference; RBC, red blood cell; RR, relative risk.

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