SUPPLEMENTARY INFORMATION

Excess mortality among non-COVID-19 surgical patients attributable to the exposure of French intensive and intermediate care units to the pandemic

This supplementary information has been provided by the authors to give readers additional information about their work.

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sMethod 1. French standards for definition of ICU/IMCU*

Intensive Care Units (ICU) manage patients presenting or at risk of presenting life-threatening organ failure, either hemodynamic, renal or respiratory. These patients need extended life-sustaining procedures such as invasive ventilation, hemodynamic support, or kidney replacement therapy. The French law formally recommends two nurses per five patients within the ICU.

Intermediate Care Units (IMCU) manage patients at risk of presenting organ failure requiring close monitoring or with unstable health status not allowing them to be discharged to a classic hospital unit. Theoretically, IMCU are not allowed to provide extended life-sustaining procedures such as invasive ventilation. IMCUs constitute intermediate levels of care at hospitals, between ICUs and classical care units. While no legal rules exist, one nurse per five patients is common within IMCU.

ICU traditionally admit either medical or surgical patients urgently needing life-sustaining procedures, while IMCU are mainly dedicated to planned postoperative care and monitoring of surgical patients. However, differences between ICU and IMCU were not as marked during times of pandemic surges and varied across French hospitals that adapted over time depending on the level of COVID-19 exposure in their own beds. ICU bed capacity therefore increased as needed by equipping and staffing IMCU beds appropriately, and additional IMCU bed capacity potentially occurred by temporary upgrading beds in classical care units.

* Journal Officiel de la République Française- (2003) Circulaire DHOS/SDO n° 2003-413 du 27 août 2003 relative aux établissements de santé publics et privés pratiquant la réanimation, les soins intensifs et la surveillance continue [Légifrance 2003] https://solidarites-sante.gouv.fr/fichiers/bo/2003/03-45/a0453485.htm. Accessed 3 January 2023.

sMethod 2. Introduction to the triple-difference design

The triple-difference design (or DDD for difference-in-differences-in-differences) is an extension of the usual double-difference design (or DD for differences-in-differences) and is employed to add a 3rd dimension of comparison. In our study, the three dimensions were the time (2020 versus 2019, first difference), the pandemic exposure (high versus moderate and versus low-or-no exposure, second difference) and the semester (semester 2 [Jul-Dec] versus semester 1 [Jan-Jun], third difference).

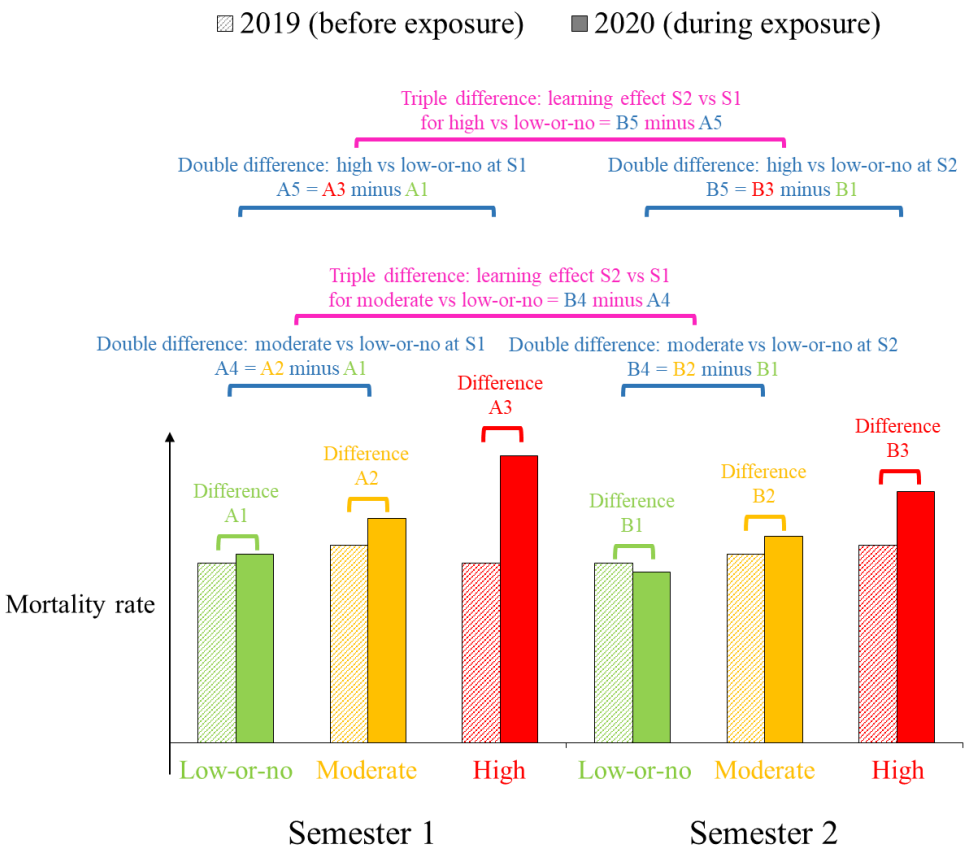


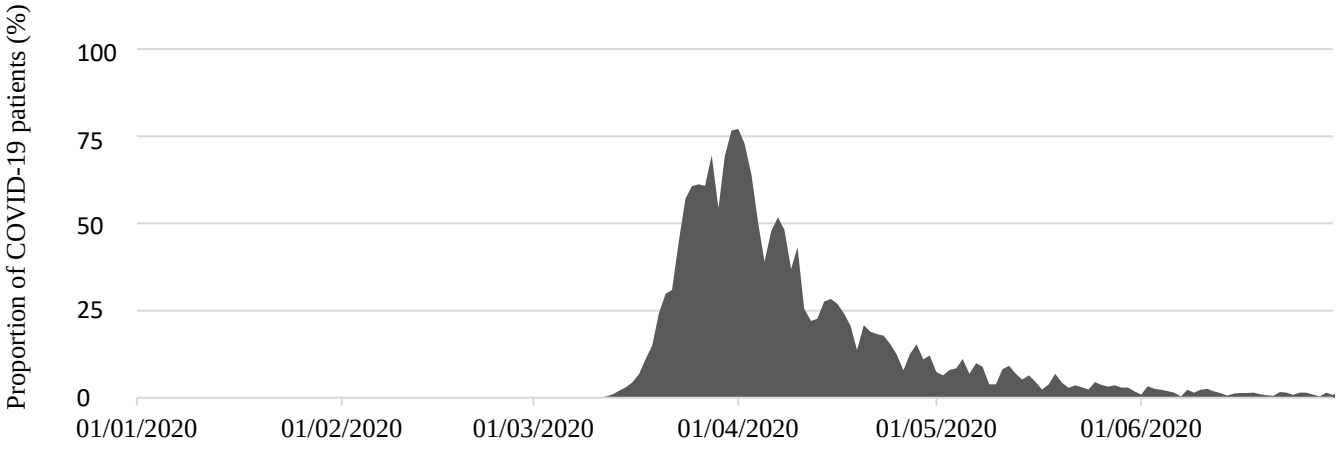
Figure: *Triple-difference design between 2019 and 2020, COVID-19 exposure groups and semester*

First difference (time): we compared the change in mortality after versus before the pandemic (2020 versus 2019) within every exposure group (high, moderate, and low-to-no) using adjusted Odds Ratios (ORs) derived from the estimates of the triple-difference model. An OR greater than one indicated an increase in mortality risk for patients among a specific exposure group in 2020 compared to the pre-pandemic 2019 period. These ORs correspond to the first level of differences colored in green, yellow and red in the figure (A1, A2, A3, B1, B2 and B3).

Second difference (pandemic exposure): we compared the change in mortality after versus before the pandemic (2020 versus 2019) between two exposure groups (high versus low-to-no, and moderate versus low-to-no) using adjusted Ratios of Odds Ratios (RORs) derived from the estimates of the triple-difference model. A ROR greater than one indicated an increase in mortality risk for patients in a given exposure group in comparison to the exposure reference. These RORs correspond to the second level of differences colored in blue in the figure (A4, B4, A5, B5).

Third difference (semester): we compared the change in mortality after versus before the pandemic (2020 versus 2019) between two exposure groups (high versus low-to-no, and moderate versus low-to-no) from one semester to the other (second versus first semester), using adjusted Ratios of Ratios of Odds Ratios (RRORs) derived from the estimates of the triple-difference model. A RROR less than one indicated a decrease in mortality risk for patients during the second semester against the first, hence a learning effect with significant improvement. These RRORs correspond to the third level of differences colored in pink in the figure.

sMethod 3. Construction of the pandemic exposure variable for patients operated at a given hospital



Non-COVID-19 Patient	Stay	Median pandemic exposure	Year	Categories of median pandemic exposure
A	08/03/2020 – 12/03/2020	2%	2020	Low exposure (< 30%)
B	29/03/2020 – 02/04/2020	70%	2020	High exposure (≥ 60%)
C	12/04/2020 – 16/04/2020	34%	2020	Moderate exposure (≥ 30% and < 60%)
D	04/03/2019 – 12/03/2019	1%	2019 (Projected exposure)	Low exposure (< 30%)
E	24/03/2019 – 01/04/2019	68%	2019 (Projected exposure)	High exposure (≥ 60%)

Stays in 2019: 'mirrored' exposure Stays in 2020: 'true' exposure

The daily proportion of COVID-19 patients among all patients treated in the ICU/IMCU (intensive or intermediate care units) of a given hospital (defined as pandemic exposure) is plotted between Jan 1, 2020 and Jun 30, 2020. We indicated the median pandemic exposure for five non-COVID-19-symptomatic patients (patients "A" to "E") who underwent a surgery in this hospital and who would potentially have needed to be admitted to the ICU/IMCU following their surgeries. Pandemic exposure for the non-COVID-19 2020 patients corresponded to the median of the daily pandemic exposure in the hospital ICU/IMCU during their stay, whether or not they were admitted to the ICU/IMCU, and was a priori categorized into three groups: low-or-no exposure less than 30%, moderate exposure between 30% and 60%, and high exposure greater than 60%. The pandemic exposure of control patients operated in 2019, before the pandemic, corresponded to a mirrored "fictive exposure" that those patients would have endured during their stay, if they had undergone surgery on the same dates and within the same hospital in 2020.

In this example, the non-COVID-19 patient "A" was hospitalized between Mar 8, 2020 and Mar 12, 2020. Because median pandemic exposure was 2% in this hospital ICU/IMCU during his/her stay, he/she was considered as a patient with low-or-no exposure in the analysis (< 30%). The non-COVID-19 patient "B" was hospitalized between Mar 29, 2020 and Apr 2, 2020. Because median pandemic exposure was 70% in that hospital ICU/IMCU during his/her stay, he/she was considered as a patient with high exposure in the analysis (≥ 60%). The non-COVID-19 patient "C" was hospitalized between Apr 12, 2020 and Apr 16, 2020. Because median pandemic exposure was 34% in that hospital ICU/IMCU during his/her stay, he/she was considered as a patient with moderate exposure in the analysis (≥ 30% and < 60%). Moreover, the non-COVID-19 patients "D" and "E" were hospitalized in the same hospital between Mar 4, 2019 and Mar 12, 2019 for the "D", and between Mar 24, 2019 and Apr 1, 2019 for the "E". Because the projected 2020 median pandemic exposure would have been respectively 1% and 68% during their stays, they were considered as patients with a low-or-no (< 30%) and high exposure (≥ 60%) respectively, in the analysis.

sTable 1. Simple, double, and triple differences in standardized in-hospital **surgical mortality rates between years, pandemic exposure groups, and semesters**

	Semester 1			Semester 2			Within Semester 1 Difference in Differences between years and pandemic exposure groups (95% CI), P value	Within Semester 2 Difference in Differences between year and pandemic exposure groups (95% CI), P value	Triple Difference between years, pandemic exposure groups, and semesters (95% CI), P value
	Observed in-hospital deaths in 2019	Observed in-hospital deaths in 2020	Difference in standardized in-hospital mortality (95% CI), P value	Observed in-hospital deaths in 2019	Observed in-hospital deaths in 2020	Difference in standardized in-hospital mortality (95% CI), P value			
All deaths									
Low-or-no exposure	8,534 (1.9%)	8,008 (2.0%)	0.0% (-0.1% to 0.1%) P=.96	8,171 (2.0%)	7,719 (1.9%)	0.0% (0.0% to 0.1%) P=.16	..	..	..
Moderate exposure	1,058 (2.4%)	696 (3.2%)	0.1% (-0.1% to 0.4%) P=.16	1,292 (2.3%)	1,229 (2.5%)	0.2% (0.0% to 0.4%) P=.03	0.2% (0.0% to 0.4%) P=.16	0.2% (0.0% to 0.4%) P=.11	0.0% (-0.3% to 0.3%) P=.88
High exposure	430 (1.9%)	259 (3.4%)	1.0% (0.6% to 1.4%) P<.001	150 (1.8%)	120 (2.0%)	0.4% (0.0% to 1.0%) P=.05	1.0% (0.6% to 1.4%) P<.001	0.4% (-0.2% to 0.9%) P=.08	-0.6% (-1.3% to 0.0%) P=.04
Inside ICU/IMCU									
Low-or-no exposure	4,897 (1.1%)	4,487 (1.1%)	0.0% (-0.1% to 0.0%) P=.47	4,724 (1.1%)	4,337 (1.1%)	0.0% (0.0% to 0.1%) P=.54	..	..	..
Moderate exposure	668 (1.5%)	358 (1.7%)	-0.1% (-0.3% to 0.2%) P=.20	701 (1.2%)	593 (1.2%)	0.1% (-0.1% to 0.3%) P=.38	-0.1% (-0.3% to 0.2%) P=.29	0.1% (-0.1% to 0.2%) P=.52	0.2% (-0.1% to 0.4%) P=.24
High exposure	282 (1.2%)	118 (1.5%)	0.3% (0.0% to 0.9%) P=.05	82 (1.0%)	37 (0.6%)	-0.1% (-0.6% to 0.5%) P=.81	0.3% (0.0% to 0.9%) P=.04	-0.1% (-0.6% to 0.5%) P=.86	-0.4% (-1.0% to 0.3%) P=.30
Outside ICU/IMCU									
Low-or-no exposure	3,637 (0.8%)	3,521 (0.9%)	0.0% (0.0% to 0.1%) P=.46	3,447 (0.8%)	3,382 (0.8%)	0.0% (0.0% to 0.1%) P=.19	..	..	..
Moderate exposure	390 (0.9%)	338 (1.6%)	0.2% (0.0% to 0.4%) P<.001	591 (1.0%)	636 (1.3%)	0.1% (0.0% to 0.3%) P=.03	0.2% (0.0% to 0.4%) P=.002	0.1% (0.0% to 0.2%) P=.09	-0.1% (-0.3% to 0.2%) P=.26
High exposure	148 (0.6%)	141 (1.8%)	0.7% (0.3% to 1.0%) P<.001	68 (0.8%)	83 (1.4%)	0.3% (0.0% to 0.7%) P=.03	0.7% (0.3% to 0.9%) P<.001	0.3% (0.0% to 0.7%) P=.04	-0.3% (-0.8% to 0.1%) P=.08

Data are n (%).

ICU/IMCUs were defined as intensive or intermediate care units.

These absolute differences in standardized rates were calculated using estimated regression coefficients obtained from the triple-difference GEE models and a marginal standardization method. They represent the Absolute Differences in standardized Rates between 2020 and 2019 per semester in each pandemic exposure group (low-or-no [0%-30%[, moderate [30%-60%[, and high [60%-100%]). The corresponding 95% confidence intervals were computed from non-parametric bootstrap based on 1,000 replications. P values were obtained directly from the models.

sTable 2. Excess in-hospital deaths related to the COVID-19 exposure group

Covid-19 exposure		Semester 1	Semester 2	Full year
Low-or-no [0-30%[	Surgical volume in 2020	392,211	402,805	795,016
	In-hospital mortality in 2020			
	Deaths	8,008	7,719	15,727
	Inside ICU/IMCU deaths	4,497	4,337	8,824
	Outside ICU/IMCU deaths	3,521	3,382	6,903
Moderate [30-60%[	Surgical volume in 2020	21,534	48,430	69,964
	In-hospital mortality in 2020			
	Deaths	696	1,229	1,925
	Inside ICU/IMCU deaths	358	593	951
	Outside ICU/IMCU deaths	338	636	974
	Deaths in excess			
	Deaths	48 (-26 to 116)	98 (-11 to 197)	147 (17 to 269)
	Inside ICU/IMCU deaths	-30 (-87 to 23)	27 (-53 to 100)	-2 (-108 to 86)
	Outside ICU/IMCU deaths	75 (28 to 121)	73 (1 to 146)	148 (65 to 238)
	Share of deaths in excess			
	Deaths	6.9% (-3.8% to 16.7%)	8.0% (-0.9% to 16.0%)	7.6% (0.9% to 16.7%)
	Inside ICU/IMCU deaths	-8.2% (-24.4% to 6.3%)	4.6% (-8.9% to 16.8%)	-0.2% (-11.3% to 9.1%)
	Outside ICU/IMCU deaths	22.3% (8.4% to 35.7%)	11.5% (0.1% to 23.0%)	15.2% (6.7% to 24.4%)
High [60-100%]	Surgical volume in 2020	7,716	6,109	13,825
	In-hospital mortality in 2020			
	Deaths	259	120	379
	Inside ICU/IMCU deaths	118	37	155
	Outside ICU/IMCU deaths	141	83	224
	Deaths in excess			
	Deaths	93 (59 to 130)	21 (-6 to 48)	114 (69 to 159)
	Inside ICU/IMCU deaths	25 (0 to 50)	-2 (-19 to 15)	23 (-8 to 53)
	Outside ICU/IMCU deaths	70 (45 to 98)	24 (0 to 47)	94 (59 to 133)
	Share of deaths in excess			
	Deaths	35.9% (22.8% to 50.0%)	17.4% (-5.1% to 40.3%)	30.0% (18.3% to 42.0%)
	Inside ICU/IMCU deaths	21.1% (0.2% to 42.4%)	-5.0% (-51.4% to 39.7%)	14.9% (-5.1% to 34.1%)
	Outside ICU/IMCU deaths	49.6% (31.6% to 69.4%)	29.2% (0.2% to 57.1%)	42.1% (26.4% to 59.2%)
Moderate + High [30-100%]	Surgical volume in 2020	29,250	54,539	83,789
	In-hospital mortality in 2020			
	Deaths	955	1,349	2,304
	Inside ICU/IMCU deaths	476	630	1,106
	Outside ICU/IMCU deaths	479	719	1,198
	Deaths in excess			
	Deaths	141 (60 to 220)	119 (5 to 220)	260 (120 to 393)
	Inside ICU/IMCU deaths	-5 (-71 to 54)	26 (-58 to 98)	21 (-91 to 116)
	Outside ICU/IMCU deaths	145 (91 to 200)	97 (19 to 176)	242 (145 to 336)
	Share of deaths in excess			
	Deaths	14.8% (6.2% to 23.1%)	8.8% (0.4% to 16.3%)	11.3% (5.2% to 17.0%)
	Inside ICU/IMCU deaths	-1.0% (-14.9% to 11.3%)	4.1% (-9.2% to 15.5%)	1.9% (-8.2% to 10.5%)
	Outside ICU/IMCU deaths	30.3% (19.1% to 41.7%)	13.5% (2.7% to 24.5%)	20.2% (12.1% to 28.0%)

ICU/IMCUs were defined as intensive or intermediate care units.

Excess deaths in the moderate and high exposure groups were calculated in comparison to the low-or-no exposure group. They were calculated separately and subsequently summed. Using the RORs (ratios of odds ratios) obtained from the triple-difference GEE models, we calculated the etiologic fraction, i.e. the share of deaths that would have been avoided if the exposure was low-or-no, and multiplied this value by the observed number of deaths in 2020.

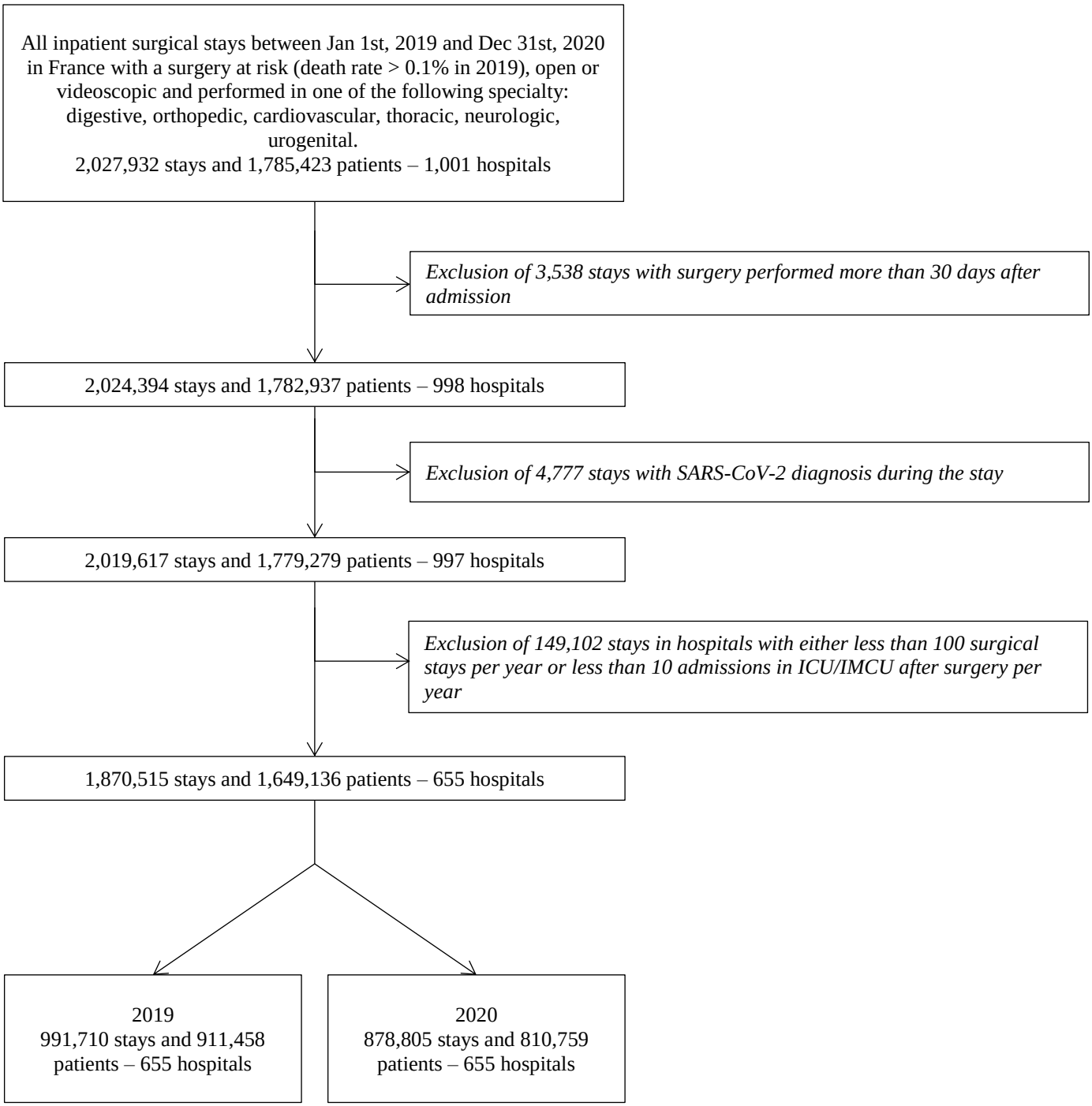
The corresponding 95% confidence intervals were computed from non-parametric bootstrap based on 1,000 replications.

Inside and outside ICU/IMCU excess deaths might not exactly sum to the total excess deaths because of the use of a different model for each outcome.

sTable 3. Characteristics of surgical inpatient stays by pandemic exposure group – stratified on subpopulation of **postoperative deaths inside versus outside ICU/IMCU**

	Surgical stays with postoperative death in 2020					
	Low-or-no Covid-19 exposure[a] [0%-30%[		Moderate Covid-19 exposure[a] [30%-60%[		High Covid-19 exposure[a] [60%-100%]	
	Death inside ICU/IMCU	Death outside ICU/IMCU	Death inside ICU/IMCU	Death outside ICU/IMCU	Death inside ICU/IMCU	Death outside ICU/IMCU
Characteristic	**n=8824**	**n=6903**	**n=951**	**n=974**	**n=155**	**n=224**
Mean patient age (years)	71.3 (13.3)	79.8 (12.6)	70.2 (13.0)	80.2 (12.3)	70.3 (13.5)	80.6 (11.6)
Male patient sex (%)	63.1	54.1	63.5	53.1	59.4	54.9
Mean patient household income (k€)[c]	21.7 (3.5)	21.7 (3.4)	21.8 (4.0)	22.0 (3.7)	22.5 (4.6)	22.9 (5.0)
Mean patient Elixhauser (score)	5.4 (3.1)	5.2 (3.0)	5.3 (3.2)	5.0 (3.0)	5.4 (3.3)	5.0 (3.3)
Mean patient hospital frailty risk (score)	11.3 (8.2)	13.5 (9.7)	11.1 (8.1)	12.8 (9.4)	10.0 (7.6)	13.2 (9.8)
Emergency admission (%)	43.6	55.0	55.1	63.1	52.9	62.9
Surgical procedure specialty (%)						
Cardiovascular	29.8	12.4	24.2	9.9	27.7	7.1
Digestive	42.8	33.7	51.1	39.4	52.3	34.4
Neurological	7.5	4.4	5.2	3.4	3.9	1.8
Orthopaedic	12.4	42.2	12.3	42.9	14.2	49.1
Thoracic	5.1	5.0	4.7	3.2	1.3	3.6
Urogenital	2.4	2.3	2.5	1.2	0.6	4.0
Surgical procedure access (%)						
Open	94.4	91.3	93.6	91.4	96.8	93.3
Videoscopic	5.6	8.7	6.4	8.6	3.2	6.7
Surgical procedure severity[d] (%)						
1	7.0	7.2	5.3	6.6	4.5	6.7
2	13.5	14.1	11.4	14.0	9.7	14.3
3	17.5	17.1	17.2	14.0	11.6	9.8
4	62.0	61.7	66.1	65.5	74.2	69.2

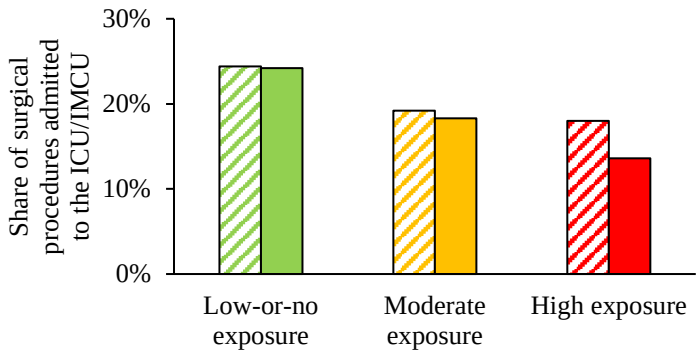
sFigure 1. Study flowchart



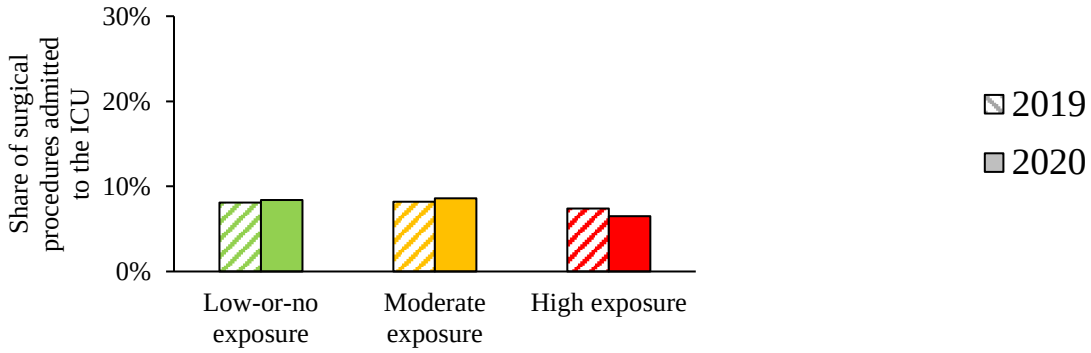
Among the 1,870,515 stays, 72,616 (3.9%) had missing median household incomes. Missing values were subsequently imputed using the median value observed per year in the hospital.

sFigure 2. Share of surgical procedures admitted to the ICU/IMCU by pandemic exposure group

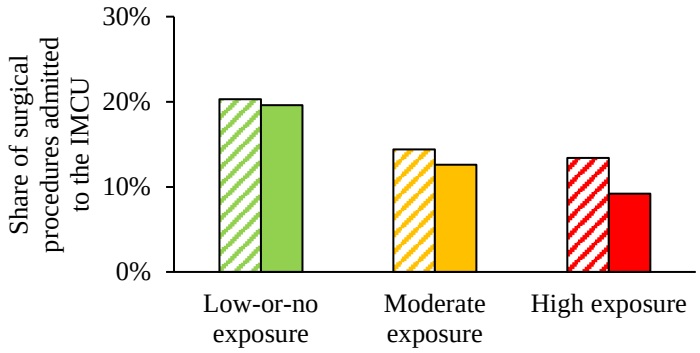
2A. ICU/IMCU admission after surgery



2B. ICU admission after surgery



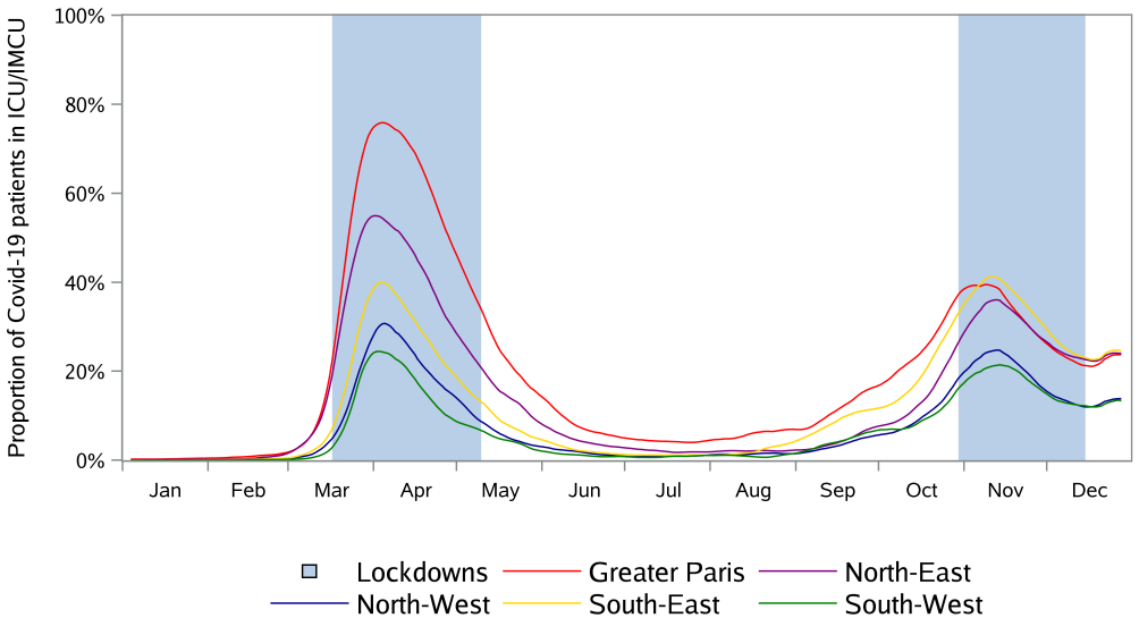
2C. IMCU admission after surgery



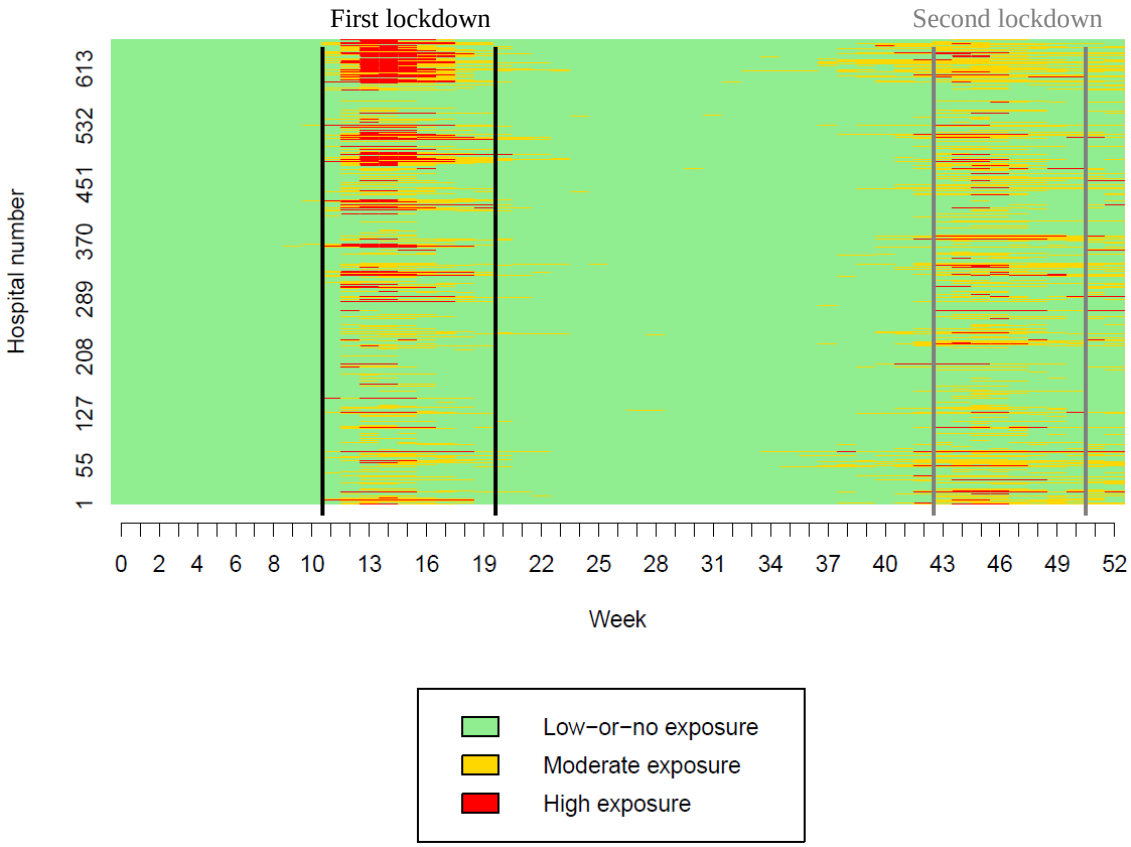
ICU/IMCUs were defined as intensive or intermediate care units.

The bar chart represents the share of surgeries with ICU/IMCU access (4a), ICU access (4b) and IMCU access (4c) between years by Pandemic Exposure Group.

sFigure 3A. Change in exposure to COVID-19 in ICU/IMCU over time per region



sFigure 3B. Change in exposure to COVID-19 in ICU/IMCU over time per hospital

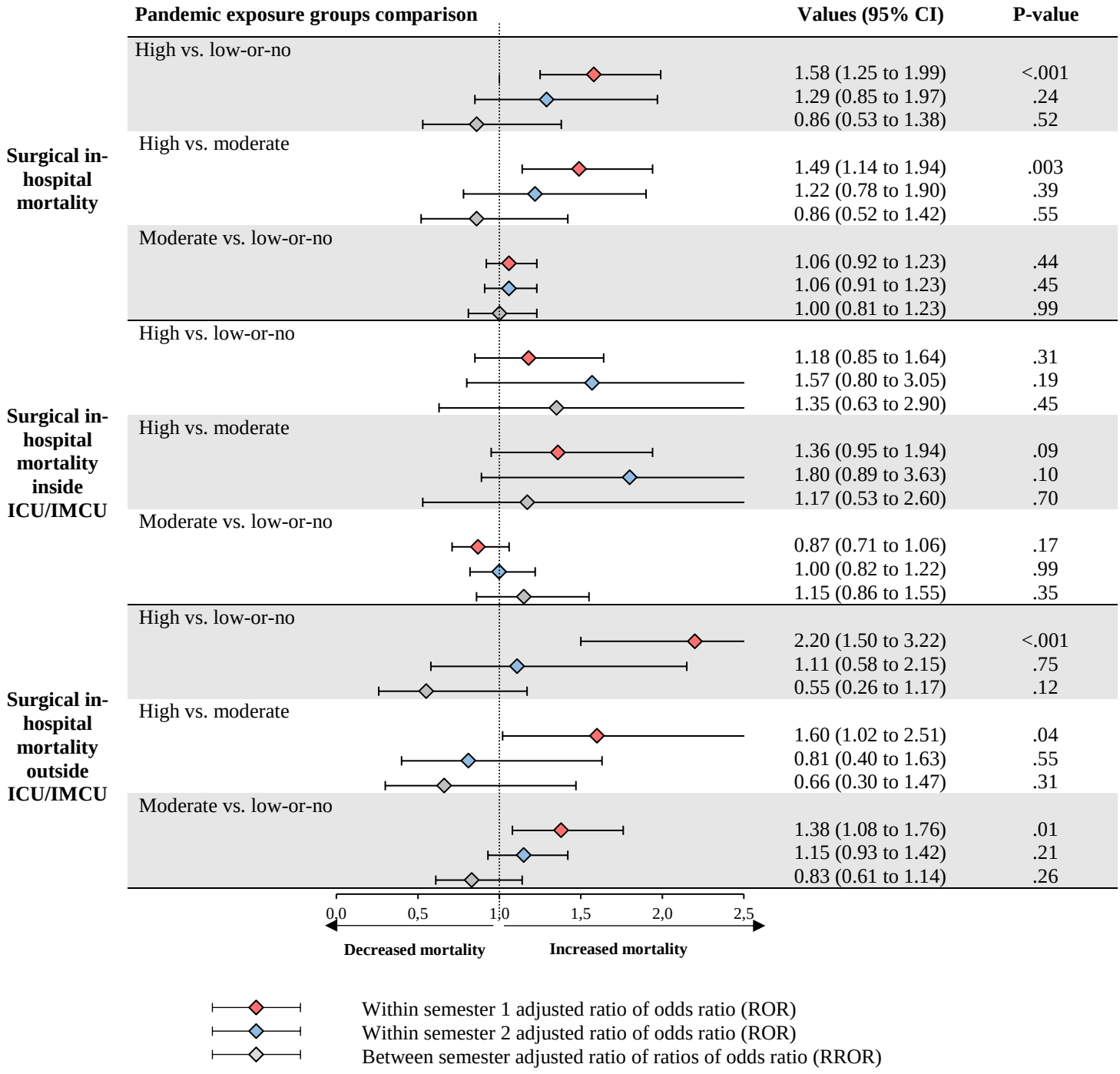


ICU/IMCUs were defined as intensive or intermediate care units.

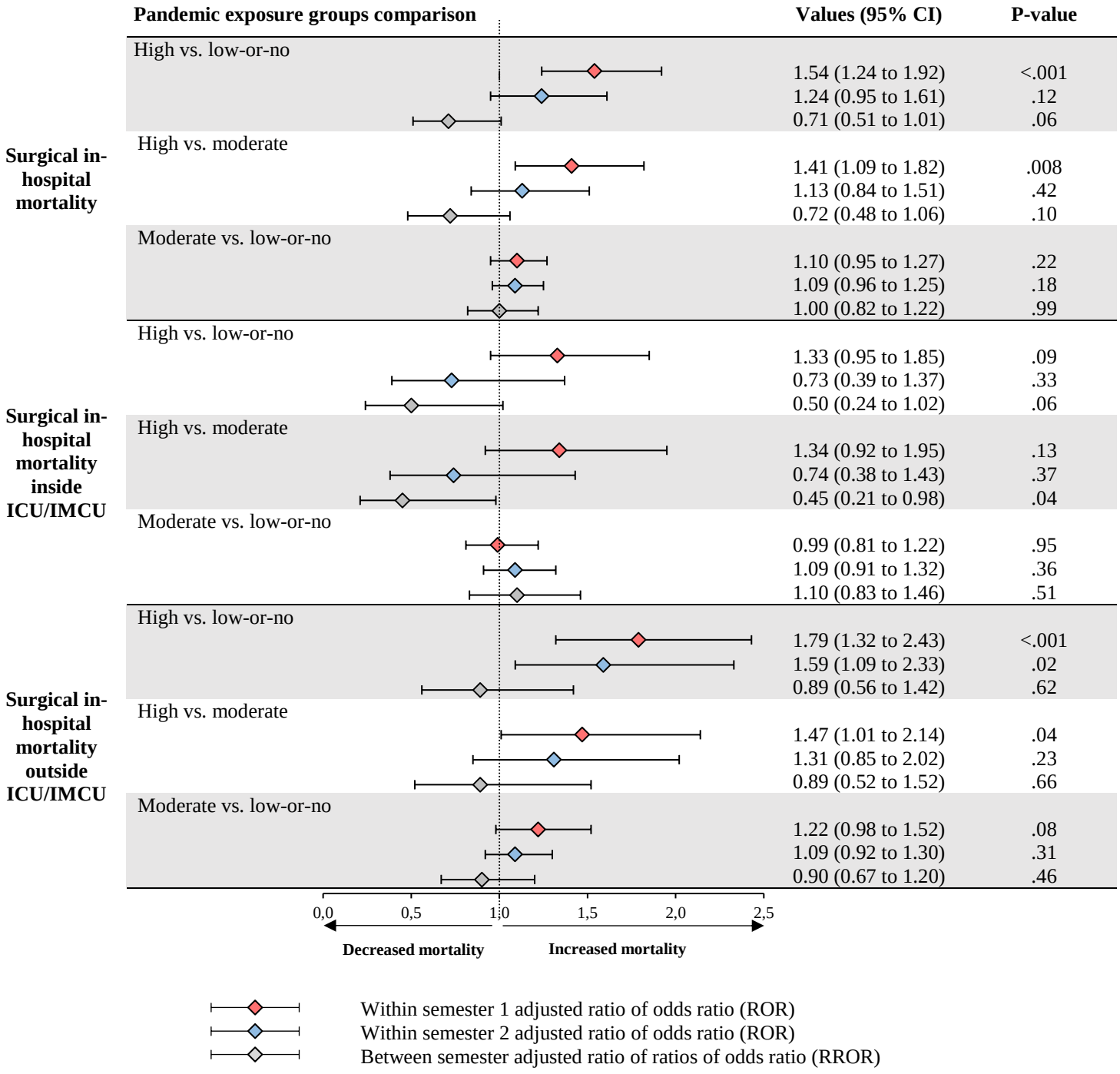
Values in sFigure 3A. are 7-day moving averages of the proportion of COVID-19 patients in ICU/ICMU per region, plotted from January to December 2020. Bands mark the two periods of national lockdowns in France. The first lockdown took place from Mar 17 to May 10, 2020, and the second from Oct 30 to Dec 15, 2020.

The sequence index plot in sFigure 3B. represents the COVID-19 pandemic exposure category per week along the year 2020 for each hospital (n=655), with one line corresponding to a single hospital. The first lockdown occurred between weeks 11 and 19 (marked with vertical black lines), and the second between weeks 43 and 50 (marked with vertical grey lines). This chart was generated using the R package ‘TraMineR’.

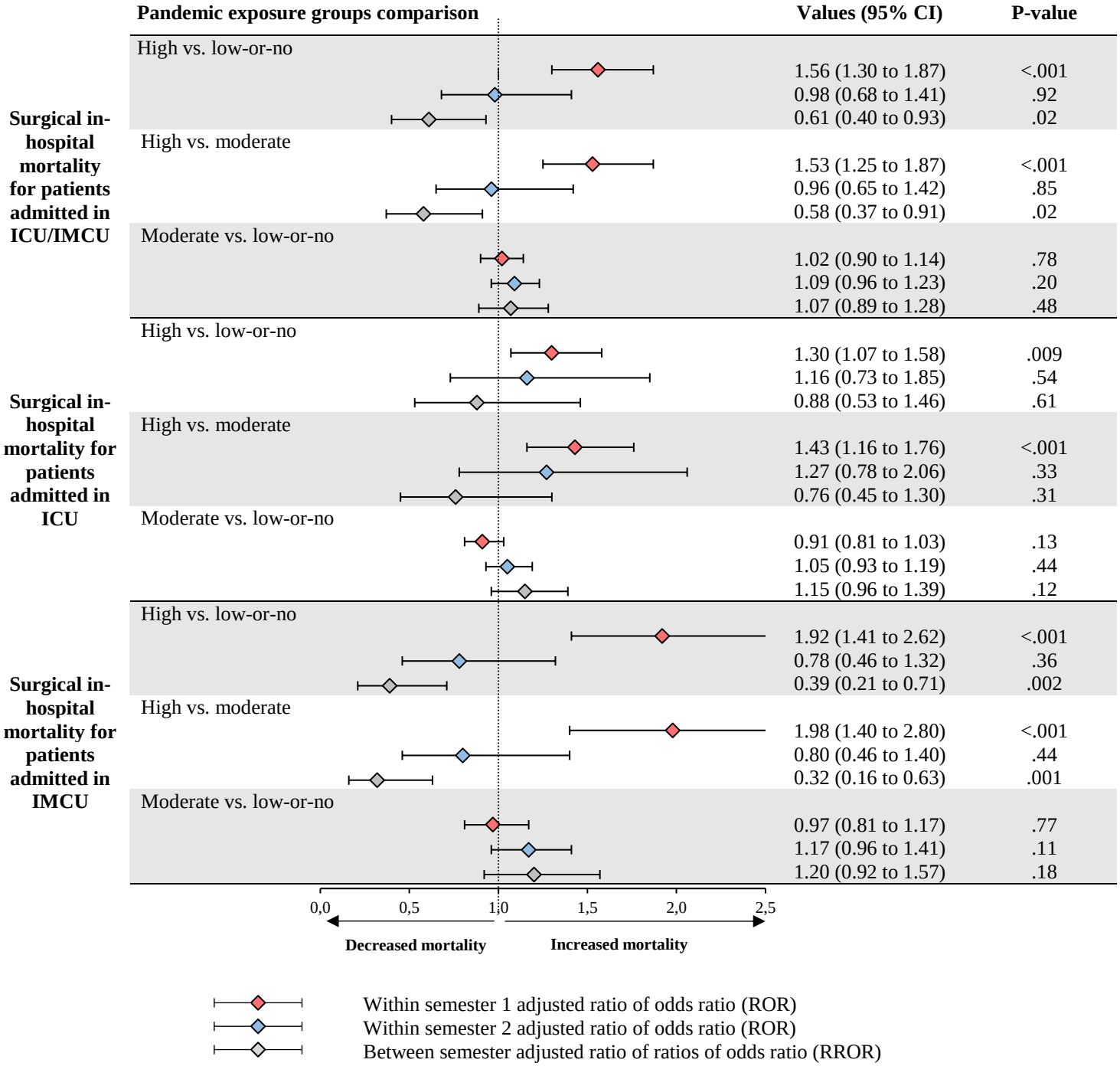
sFigure 4A: Comparison of in-hospital surgical mortality risk between pandemic exposure groups by semester with related learning effect - stratified on subpopulation of elective surgeries



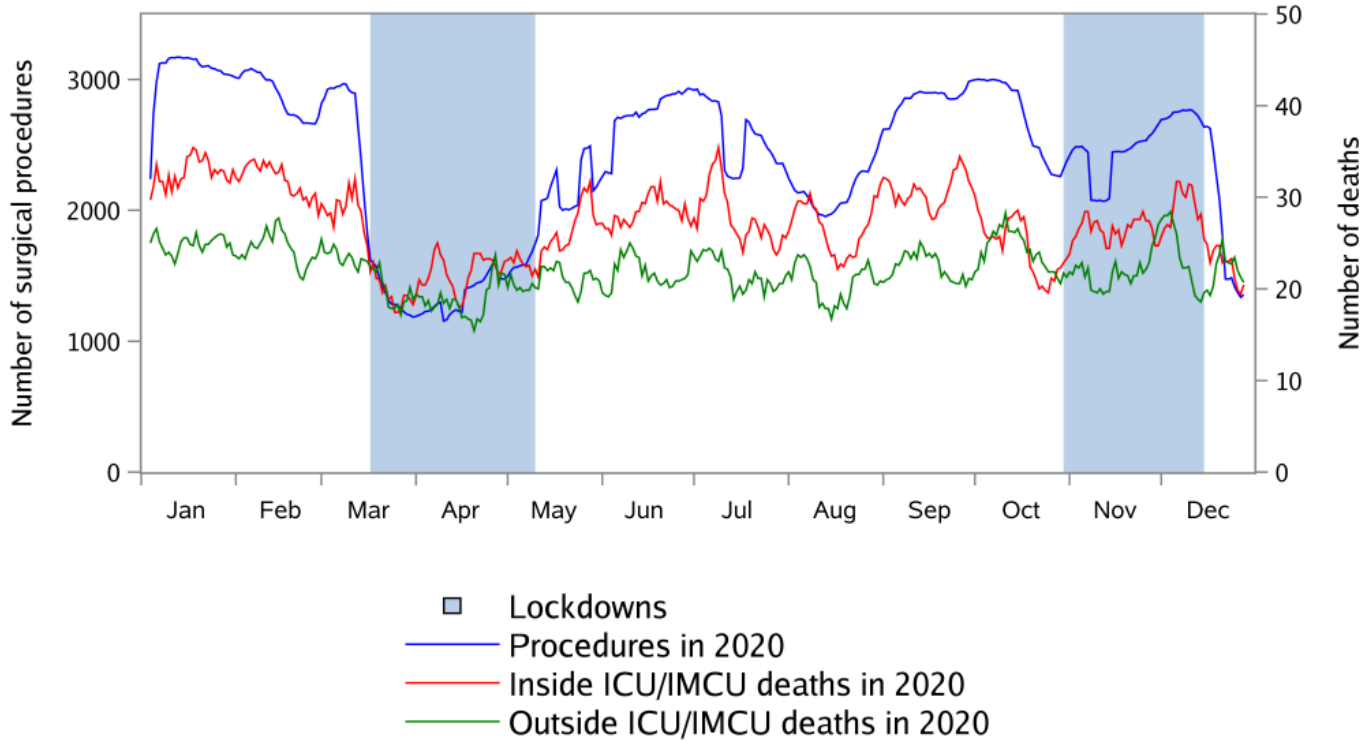
sFigure 4B: Comparison of in-hospital surgical mortality risk between pandemic exposure groups by semester with related learning effect - stratified on subpopulation of emergency surgeries



sFigure 4C: Comparison of in-hospital surgical mortality risk between pandemic exposure groups by semester with related learning effect - stratified on subpopulations of patients admitted in ICU/IMCU, ICU and IMCU



sFigure 5. Number of surgical procedures and deaths in 2020, inside and outside ICU/ICMU



ICU/IMCUs were defined as intensive or intermediate care units.

Values in sFigure 5. are 7-day moving averages of the number of surgical procedures and the numbers of deaths inside versus outside ICU/IMCU, plotted from January to December 2020. Bands mark the two periods of national lockdowns in France. The first lockdown took place from Mar 17 to May 10, 2020, and the second from Oct 30 to Dec 15, 2020.