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Original Article

Postoperative mortality and complications in patients with and without pre-operative SARS-CoV-2 infection: a service evaluation of 24 million linked records using OpenSAFELY

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Summary

Surgical decision-making after SARS-CoV-2 infection is influenced by the presence of comorbidity, infection severity and whether the surgical problem is time-sensitive. Contemporary surgical policy to delay surgery is informed by highly heterogeneous country-specific guidance. We evaluated surgical provision in England during the COVID-19 pandemic to assess real-world practice and whether deferral remains necessary. Using the OpenSAFELY platform, we adapted the COVIDSurg protocol for a service evaluation of surgical procedures that took place within the English NHS from 17 March 2018 to 17 March 2022. We assessed whether hospitals adhered to guidance not to operate on patients within 7 weeks of an indication of SARS-CoV-2 infection. Additional outcomes were postoperative all-cause mortality (30 days, 6 months) and complications (pulmonary, cardiac, cerebrovascular). The exposure was the interval between the most recent indication of SARS-CoV-2 infection and subsequent surgery. In any 6-month window, < 3% of surgical procedures were conducted within 7 weeks of an indication of SARS-CoV-2 infection. Mortality for surgery conducted within 2 weeks of a positive test in the era since widespread SARS-CoV-2 vaccine availability was 1.1%, declining to 0.3% by 4 weeks. Compared with the COVIDSurg study cohort, outcomes for patients in the English NHS cohort were better during the COVIDSurg data collection period and the pandemic era before vaccines became available. Clinicians within the English NHS followed national guidance by operating on very few patients within 7 weeks of a positive indication of SARS-CoV-2 infection. In England, surgical patients' overall risk following an indication of SARS-CoV-2 infection is lower than previously thought.

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Introduction

Surgical decision-making after SARS-CoV-2 infection is influenced by the presence of comorbidity, infection severity and whether the surgical problem is time-sensitive [1]. The COVIDSurg collaborative conducted the largest prospective study on surgical outcomes after SARS-CoV-2 infection to date, showing increased postoperative mortality and pulmonary complications up to 7 weeks following a positive test in patients who had recovered fully [2]. This study was conducted before vaccines [3] or evidence-based drug therapy for severe COVID-19 [4] became available. However, UK [5] and German [6] guidance still recommends deferring elective surgery for 7 weeks after SARS-CoV-2 infection. In contrast, current guidance in the USA recommends 7 weeks of postponement in unvaccinated individuals only [7]. Guidance from Australia and New Zealand recommends stratification by surgical magnitude, with postponement ranging from 4 weeks for minor to 12 weeks for major surgery [8].

Contemporary surgical policy-making is, therefore, constrained by very heterogeneous global guidance. A paucity of studies in highly vaccinated populations has been identified as a limiting factor for evidence-based policy-making in the USA [7], Germany [6], Australia and New Zealand [8]. It is also unclear as to what extent the above guidance is followed, and how possible variance in enactment is associated with outcomes. Scheduling constraints might also be a factor, limiting the capacity of health services to clear the post-pandemic backlog of cancer and other elective surgery [7, 9].

Postponement of potentially curative cancer surgery can worsen overall survival. A meta-analysis of studies conducted before 2020 found that a 12-week delay to surgery was associated with decreased overall survival in early-stage breast, lung and colon cancer [10]. In patients with non-cancer pathology such as osteoarthritis, further postponement of surgical intervention on the background of already long waiting lists has been identified as exposing patients to continuing suffering, potentially worse long-term outcomes and increased long-term opioid use [11].

In this context, we identified a need to evaluate the provision of timely and safe surgery during the COVID-19 pandemic before and after vaccines became available. We conducted a retrospective observational study of 24 million linked primary and secondary care records across England. Our aims were to establish to what extent English hospitals scheduled surgery within 7 weeks from a SARS-CoV-2 diagnosis and describe postoperative outcomes, stratified by time between surgery and a SARS-CoV-2 infection, or no infection, and surgery before and after widespread vaccine availability.

Methods

We adapted the COVIDSurg protocol [2] to account for the retrospective nature of our service evaluation. The exposure was the duration between an indication of SARS-CoV-2 infection and the patient's date of surgery. An unabridged description of our methods is given in online Supporting Information Appendix S1.

The data source was OpenSAFELY, a secure and transparent platform linking data from two major NHS primary care record providers with relevant databases from secondary care and with the UK Office of National Statistics. Linkage and analysis are conducted within the records providers' data centres (OpenSAFELY-EMIS and OpenSAFELY-TPP), meaning that researchers never see individual-level data. All data were linked, stored and analysed securely within the OpenSAFELY platform (https://www.opensafely.org). Data include pseudonymised data such as coded diagnoses, medications and physiological parameters. No free-text data are included. Only OpenSAFELY-TPP contains data on surgical events. OpenSAFELY-TPP comprises around 24 million patient records, from over 2600 general practice surgeries and a third of mental health Trusts in England, and is representative of the English population [12, 13]. All code is shared openly for review and re-use under MIT open licence (https://github.com/opensafely/surg-covid-safely). Our study population was patients who underwent surgery between 17 March 2018 and 17 March 2022. The start and end dates were chosen as being 2 y before and after the date that NHS England announced the temporary postponement of all elective surgery as part of the pandemic response [14].

This study was a service evaluation with sponsorship from NHS England and additional institutional ethical approval by the University of Leeds Faculty for Engineering and Physical Sciences Ethics Committee. NHS England is the data controller for OpenSAFELY-EMIS and OpenSAFELY-TPP and EMIS and TPP are the data processors. All study authors using OpenSAFELY had the approval of NHS England. This implementation of

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OpenSAFELY is hosted within the TPP environment, which is accredited to the ISO 27001 information security standard and is NHS IG Toolkit compliant [15].

Patient data were pseudonymised for analysis and linkage using industry standard cryptographic hashing techniques; all pseudonymised datasets transmitted for linkage onto OpenSAFELY are encrypted; access to the platform is via a virtual private network connection, restricted to a small group of researchers; the researchers hold contracts with NHS England and only access the platform to initiate database queries and statistical models; all database activity is logged; only aggregate statistical outputs leave the platform environment following best practice for anonymisation of results such as statistical disclosure control for low cell counts.

The OpenSAFELY research platform adheres to the obligations of the UK General Data Protection Regulation and the Data Protection Act 2018. In 2020, the Secretary of State for Health and Social Care used powers under the UK Health Service (Control of Patient Information) Regulations 2002 to require organisations to process confidential patient information for the purposes of protecting public health, providing healthcare services to the public, and monitoring and managing the COVID-19 outbreak and incidents of exposure; this sets aside the requirement for patient consent [16]. This was extended in November 2022 for the NHS England OpenSAFELY COVID-19 research platform [17]. In some cases of data sharing, the common law duty of confidence is met using, for example, patient consent or support from the Health Research Authority Confidentiality Advisory Group. Taken together, these provide the legal bases to link patient datasets on the OpenSAFELY platform. General practice surgeries, from which the primary care data are obtained, are required to share relevant health information to support the public health response to the pandemic, and have been informed of the OpenSAFELY analytics platform. The study was supported by Professor R. Moonesinghe (National Clinical Director for Critical and Peri-operative Care, NHS England and NHS Improvement) as senior sponsor.

Our outcomes were those used in the COVIDSurg study [2]: all-cause mortality at 30 days and 6 months postoperatively, as well as 30-day postoperative pulmonary, cardiac and cerebrovascular complications. The exposure was the interval between the most recent indication of SARS-CoV-2 infection and subsequent surgery. While COVIDSurg calculated intervals in weeks, we calculated intervals in days and modelled categorically, namely no pre-operative indication of SARS-CoV-2 infection; ≤ 14 days; 15–28 days; 29–42 days and ≥ 43 days. Pre-operative SARS-CoV-2 testing was mandatory in England between July 2020 [18] and April 2022 [16]. Pre-operative PCR tests are conducted via the UK's Pillar 1 (clinical need) route and no selection bias would be expected since all Pillar 1 test results are available in OpenSAFELY.

We stratified across the same concepts as the COVIDSurg study [2], except for the revised cardiac risk index where we stratified on the presence of cardiac or cerebrovascular disease. We did not construct multivariable regression models, to mitigate collider bias which has been found to be a risk in COVID-19-related research [19].

We did not query individuals' vaccination status at the time of surgery. Given rapid vaccination uptake and high levels of coverage in England [20], we assumed that the group who are both unvaccinated and required surgery at any time point are highly likely to be atypical in unknown ways. We also wanted to diverge from previous studies that focused on infection at the individual level in an at-risk population by providing aggregate summaries of a general population, on which general public-health policy is better based. We defined three eras for stratification (Fig. 1): era 1, pre-pandemic: 17 March 2018 to 17 March 2020. Era 2, pandemic-no-vaccine: 18 March 2020 to 12 January 2021. We chose 12 January 2021 as the end of the period when vaccination was unavailable, because the first vaccines were administered on 5 December 2020. After this date, we allowed 3 weeks for completing the vaccination schedule as was recommended at the time, followed by 2 weeks for effect [21]. Within the pandemic no-vaccine era, we defined a 4-week COVIDSurg data collection period: 5 October 2020 to 1 November 2020, coinciding with the data collection period for the COVIDSurg study [2]. Finally, era 3, pandemic-with-vaccine: 13 January 2021 to 17 March 2022.

Our unit of analysis was the surgical procedure; patients undergoing repeat surgery during the study period were considered more than once. We conducted a complete case analysis, recognising that excluding patients with missing data may introduce collider and other biases [19]. We calculated counts and percentages of patients in strata of our covariates to provide clinical context for the cohorts. In accordance with guidance from OpenSAFELY, all counts ≤ 7 were redacted before all remaining counts were rounded to the nearest multiple of 10. All proportions were calculated using these rounded counts. Counts used to calculate totals were summed before redaction and rounding, so the redacted-and-rounded sum of counts from intervals does not always match the redacted-and-rounded totals.

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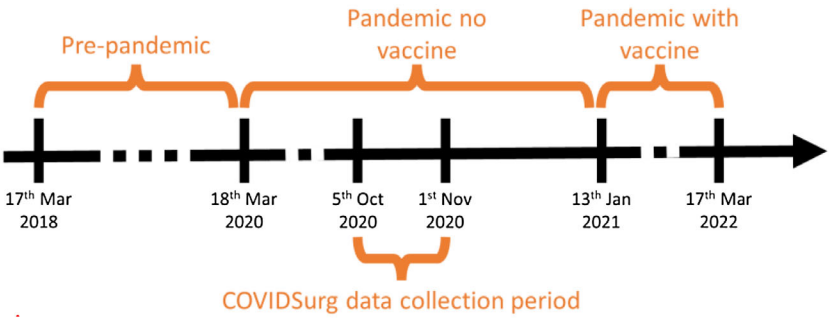

Figure 1 Timeline of key study dates (vertical black lines) that define study era (orange periods).

Data management was performed using open-source Python (v3.8.2) and R (v4.0.2), with analysis carried out using R (R Foundation, Vienna, Austria). Code for data management and analysis, as well as code lists, are archived online at https://github.com/opensafely/surg-covid-safely and www.opencodelists.org (online Supporting Information Appendix S1 and Table S1). The OpenSAFELY platform design requires that all analyses are prespecified and all revisions and database activity are publicly available.

Results

Our analysis code was run on 15 January 2023, yielding a cohort of 3,658,140 patients undergoing surgical procedures. Of these, 1,242,180 were conducted during the pandemic-with-vaccine era on patients with a mean (SD) age of 55.1 (22.4) y. Results for other eras are given in online Supporting Information Appendix S2. In any 6-month window, < 3% of surgical procedures were conducted within the 7-week threshold after a positive PCR assay suggested by the COVIDSurg study (Fig. 2). Component counts of patients in shorter intervals were so low as to breach OpenSAFELY disclosive rules. Across all time periods, a higher proportion of emergency surgery was conducted within 7 weeks of a positive SARS-CoV-2 test than elective surgery, although always < 3% of the emergency surgical caseload.

Table 1 presents patient characteristics and Table 2 presents the outcomes of the patient cohort during the pandemic-with-vaccine era. In addition to the reported outcomes, we planned to stratify by age as well as test-to-surgery interval, as was undertaken in the COVIDSurg study [2]. However, the returned counts were so low for younger patients in our cohort that they required redaction. Overall, 30-day postoperative mortality was <0.2% and 30-day postoperative complications were < 1.0%. Mortality for surgery conducted within 2 weeks of a positive test in the pandemic-with-vaccine era was 1.1% (compared with 9.1% in COVIDSurg), declining to 0.3% by 4 weeks (6.9% in

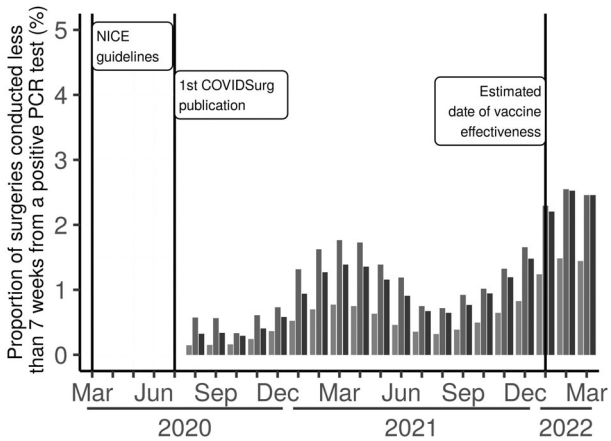

Figure 2 Proportion of surgical procedures conducted < 7 weeks (<43 days) from a positive PCR assay (see caveats in the Methods in the main text). Thin, full-length, vertical black lines indicate events of note in the timeline. The cohorts are patients who underwent surgery during elective admission (light grey) or emergency admission (dark grey), and those without a definitive admission in the record (light black).

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Table 1 Patient characteristics for those who underwent surgery stratified by duration from indication of SARS-CoV-2 infection to surgery date. Period of interest is from 12 January 2021 until 31 March 2022 (i.e. the pandemic-with-vaccines era). In accordance with guidance from OpenSAFELY, all counts ≤ 7 were redacted before all remaining counts were rounded to the nearest multiple of 10. Values are number (proportion). All proportions were calculated using these rounded counts.

		Interval between indication of infection and surgery			
	No indication of infection n = 1,121,490	**≤14 days n = 3660**	**15–28 days n = 5480**	**29–42 days n = 6250**	**≥43 days n = 105,300**
Female	628,340 (56.0%)	2230 (63.4%)	3260 (59.5%)	3740 (59.8%)	63,740 (60.5%)
Male	493,140 (43.9%)	1340 (36.6%)	2220 (40.5%)	2510 (40.2%)	41,570 (39.5%)
Chronic cardiac disease					
Yes	145,440 (13.0%)	310 (8.5%)	470 (8.6%)	520 (8.3%)	9720 (9.2%)
No	976,040 (87.0%)	3350 (91.5%)	5010 (91.4%)	5730 (97.7%)	95,590 (90.8%)
Diabetes					
Yes	203,410 (18.1%)	560 (15.3%)	780 (14.2%)	850 (13.6%)	16,460 (15.6%)
No	918,070 (81.9%)	3100 (84.7%)	4700 (85.8%)	5400 (86.4%)	88,840 (84.4%)
Chronic respiratory disease					
Yes	77,760 (6.9%)	150 (4.1%)	260 (4.7%)	320 (5.1%)	5270 (5.0%)
No	1,043,720 (93.1%)	3510 (95.9%)	5220 (95.3%)	5930 (94.9)	100,030 (95.0%)
Cerebrovascular disease					
Yes	49,300 (4.4%)	100 (2.7%)	140 (2.6%)	170 (2.7%)	3110 (3.0%)
No	1,072,190 (95.6%)	3560 (97.3%)	5340 (97.4%)	6080 (97.3%)	102,190 (97%)
Admission method					
Elective	648,120 (57.8%)	1310 (35.8%)	2420 (44.2%)	2910 (46.6%)	55,300 (52.5%)
Emergency	18,180 (1.6%)	130 (3.6%)	110 (2.0%)	120 (11.9%)	1940 (1.8%)
Unknown	455,220 (40.6%)	2220 (60.7%)	2960 (54.0%)	3220 (51.5%)	48,060 (45.6%)

Table 2 Outcomes for patients who underwent surgery stratified by duration from indication of SARS-CoV-2 infection to surgery date. Period of interest is from 12 January 2021 until 31 March 2022 (i.e. the pandemic-with-vaccines era). In accordance with guidance from OpenSAFELY, all counts ≤ 7 were redacted before all remaining counts were rounded to the nearest multiple of 10. All proportions were calculated using these rounded counts. Values are number (proportion).

		Interval between indication of infection and surgery			
	No indication of infection n = 1,121,490	**≤14 days n = 3660**	**15–28 days n = 5480**	**29–42 days n = 6250**	**≥43 days n = 105,300**
30-day postoperative mortality					
Alive within 30 days	1,119,280 (99.8%)	3610 (98.6%)	5450 (99.5%)	6230 (99.7%)	105,120 (99.8%)
Dead within 30 days	2200 (0.2%)	40 (1.1%)	30 (0.5%)	20 (0.3%)	190 (0.2%)
6-month postoperative mortality					
Alive within 6 months	1,106,580 (98.7%)	3550 (97.0%)	5370 (98.0%)	6160 (98.6%)	104,230 (99.0%)
Dead within 6 months	14,910 (1.3%)	110 (3.0%)	110 (2.0%)	90 (1.4%)	1070 (1.0%)
30-day postoperative pulmonary complications					
No complications	1,119,680 (99.8%)	3600 (98.4%)	5440 (99.3%)	6230 (99.7%)	150,130 (99.8%)
Complications	1800 (0.2%)	60 (1.6%)	40 (0.7%)	20 (0.3%)	180 (0.2%)
30-day postoperative cardiac complications					
No complications	1,111,290 (99.1%)	3600 (98.4%)	5410 (98.7%)	6180 (98.9%)	104,560 (99.3%)
Complications	10,190 (0.9%)	60 (1.6%)	70 (1.3%)	70 (1.1%)	740 (0.7%)
30-day postoperative cerebrovascular complication					
No complications	1,120,280 (99.9%)	3650 (99.7%)	5470 (99.8%)	6240 (99.8%)	105,230 (99.9%)
Complications	1210 (0.1%)	Redacted	10 (0.2%)	10 (0.2%)	80 (0.1%)

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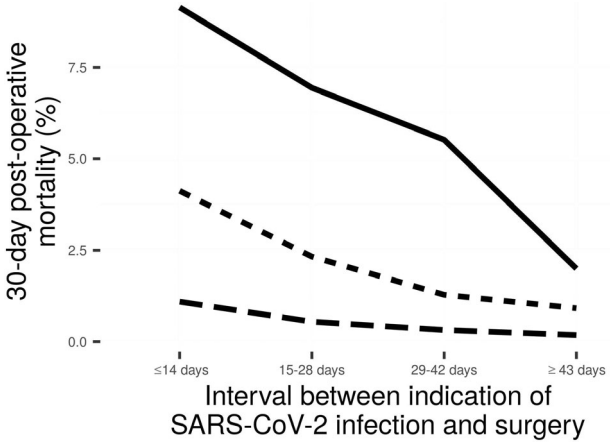

Figure 3 Thirty-day postoperative mortality in the COVIDSurg study, solid line; the OpenSAFELY pandemic-no-vaccine era, short-dashed line; and the OpenSAFELY pandemic-with-vaccine era, long dashed line. OS, OpenSAFELY dataset.

Table 3 Thirty-day postoperative mortality across eras, across all intervals defined by the interval between an indication of SARS-CoV-2 infection patients' surgery date. In accordance with guidance from OpenSAFELY, all counts ≤ 7 were redacted before all remaining counts were rounded to the nearest multiple of 10. All proportions were calculated using these rounded counts. Values are counts of deaths (n), column totals (N) and proportion.

					Interval between indication of infection and surgery							
Era	**Total n/N**		**No indication of infection n/N**		**≤14 days n/N**		**15–28 days n/N**		**29–42 days n/N**		**≥43 days n/N**	
Pre-pandemic	2470/1,918,850	0.1%	-	-	-	-	-	-	-	-	-	-
Pandemic-no-vaccines	1710/497,110	0.3%	1620/491,220	0.3%	40/970	4.1%	20/860	2.3%	10/780	1.3%	30/3280	0.9%
Pandemic-with-vaccines	2480/1,242,180	0.2%	2200/1,121,490	0.2%	40/3660	1.1%	30/5480	0.5%	20/6250	0.3%	190/105,300	0.2%
COVIDSurg data collection period (OpenSAFELY)	150/67,580	0.2%	140/66,980	0.2%	Redacted	-	0/80	0.0%	0/50	0.0%	Redacted	-
COVIDSurg data collection period (COVIDSurg Collaborative)	2151/140,231	1.5%	1973/137,104	1.4%	104/1138	9.1%	32/461	6.9%	18/326	5.5%	24/1202	2.0%

COVIDSurg). Compared with the COVIDSurg study cohort, outcomes in this OpenSAFELY cohort were better during the COVIDSurg data collection period and the pandemic-no-vaccine era (Fig. 3; Table 3).

Discussion

We describe the service provided by the English NHS during the COVID-19 pandemic with a focus on the extent to which guidance was followed. We described the proportion of surgical procedures conducted < 7 weeks from a positive PCR assay, and postoperative outcomes before and during the COVID-19 pandemic. Our service evaluation suggests that hospitals in England operated on very few patients within 7 weeks of a positive SARS-CoV-2 test (<3% of procedures between March 2020 and March 2022). We conclude that patient outcomes were better for patients receiving care in hospitals in England than the COVIDSurg global average. The group of patients operated on within 7 weeks of a positive test were so few that making risk models and further stratification would be unreliable. While the most recent UK guidelines suggest a risk-based approach to timing of surgery after SARS-CoV-2 infection, clinical experience suggests that, for all but the most urgent elective or emergency surgery, clinicians continue to postpone operations if they are scheduled within 7 weeks of an indication of SARS-CoV-2 infection. If, as our data suggest, the risk associated with surgery after indication of SARS-CoV-2 infection is much lower than previously

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thought, delaying surgery might cause more harm than good, particularly in patients who have already waited longer than desirable for surgery.

Our findings differ from those of the COVIDSurg study [2] and subsequent UK consensus guidance [5]. Outcomes among our sample of operated patients in England were substantially better than in the COVIDSurg global surgical sample. However, even before the COVIDSurg study, very few procedures in our cohort were conducted within 7 weeks of a positive test, making it likely that the cohort who were operated on were highly selected for surgical urgency, low risk or both.

Our findings are somewhat congruent with recent studies from the USA on surgery in partially vaccinated cohorts. A retrospective analysis of 228,643 patients (mean (SD) age 56.3 (16.7) y) found that, compared with a pre-pandemic group, there was a greater risk of postoperative pulmonary complications in patients not completing a primary vaccination schedule before surgery and undergoing surgery within 4 weeks of a positive test [22]. This was not observed in patients who underwent surgery more than 4 weeks since a positive test, nor in vaccinated patients regardless of duration since a positive test. A propensity-matched case–control study of partially and unvaccinated elderly American veterans (median age 72 y and 71 y, respectively) undergoing surgery observed that patients who were partially vaccinated experienced fewer SARS-CoV-2 infections, pulmonary complications and thromboembolic events [23]. Neither of these studies provide justification for their statistical adjustments [19]. In contrast, we did not assume that completing a primary schedule confers a `vaccinated´ status to stratify on. It is recognised that repeated vaccination is required to maintain the varied protection against severe COVID-19 [24, 25] and any apparent relationship between individual vaccination status and outcome is likely to be confounded by the growing proportion of patients receiving both vaccinations and sustaining repeated infection, changes in the predominant virus variants and improved treatment for severe COVID-19 [5].

In a diversion from the COVIDSurg collaborative studies, we did not undertake regression analysis, to avoid the possibility of the so-called `Table 2 fallacy´ where biases are introduced by the analysis [24]. This has previously been an issue necessitating reversal of French national policy based on OpenSAFELY data [25]. We provided our stratification table like the COVIDSurg Collaborative only as a benchmark for comparison under similar biases: that is, we conducted an analysis with similar biases, but with different data. We also did not attempt to delineate a subgroup who remained symptomatic after 7 weeks, since the coding of long COVID in primary care has been found to be highly subjective, lower in OpenSAFELY-TPP than OpenSAFELY-EMIS and much lower than in symptom prevalence surveys [26]. Primary research would be needed to describe the relationship between ongoing COVID-19 symptoms and surgical outcomes.

Our study is the largest cohort study on the relationship between an indication of SARS-CoV-2 infection and surgery to date and includes the eras before and after vaccination was available. It is modelled on previous work, enabling comparison. Our analyses are highly transparent and reproducible, where we have deviated from our prespecified analyses is reported in the manuscript and discoverable via our publicly available code. The work also has important limitations. We only used records with no missing data, even though this can induce collider bias via cohort selection (20). The OpenSAFELY platform was instrumental in facilitating the analyses we conducted. Unfortunately, the approach of bringing the analysis to the data rather than the data to the analyst means that it is not possible to undertake thorough evaluations of data quality in a domain with significant data quality challenges [27].

Our results should be interpreted with some caution. The study was a service evaluation rather than generalisable research and, as such, should not be used to infer similarity to cohorts other than surgical patients within the English NHS. We recommend that other countries evaluate their surgical services to assess whether country-specific guidelines were followed, and whether interventions are still appropriate. Our findings should not be used to guide decision-making for higher-risk groups, for example, those who remain symptomatic beyond the acute phase of COVID-19 or those individuals who are immunosuppressed, because our statistics are aggregate summaries of the patient population. Pragmatic, individualised, shared decision-making remains necessary. Furthermore, although our code lists mapped well to pre-pandemic ecological analysis of surgical activity (see online Supporting Information Appendix S1), this does not represent a comprehensive view of all surgery in England. Our results are also presented unadjusted by design since statistical adjustment in the absence of a causal model may introduce bias rather than ameliorate it [19, 28].

In conclusion, this is the first large-scale analysis of surgical outcomes throughout the COVID-19 pandemic timeline. It suggests that, in the English NHS, surgical patients' overall risk following an indication of SARS-CoV-2 infection may be lower than previously thought. Clinicians followed national guidance by operating on very few

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patients within 7 weeks of a positive indication of SARS-CoV-2 infection from PCR assays. Across all eras of the pandemic to date, surgical outcomes were substantially better than previously thought, even within 7 weeks of a positive test. Given that delaying surgery is likely to worsen patient outcomes in the longer term, we recommend that UK guidelines should reduce the 7-week threshold for low-risk patients who have fully recovered after a positive SARS-CoV-2 test. A simple change in emphasis could suffice, for example, suggest that surgery is delayed for no more than 2 weeks after indication of a SARS-CoV-2 infection unless there are specific circumstances that places an individual at higher risk of poor outcomes. This would bring clinical guidance on surgical timing after an indication of SARS-CoV-2 infection into line with common practice regarding other acute respiratory infections. As our study is observational, we also recommend ongoing evaluation of the effect of any policy change that may result. Our analysis scripts would be deployable to repeat in a suitable environment, creating a near-real-time monitoring system of the effect of policy change. We also recommend that other countries evaluate their surgical services to assess whether country-specific guidelines were followed and whether interventions are still appropriate. Crucially, any change in practice needs to be in the context of a real-time evaluation as our multifaceted understanding of the physiology and epidemiology of SARS-CoV-2 improves.

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Supporting Information

Additional supporting information may be found online via the journal website.

Appendix S1. Further details on methods.

Appendix S2. Demographic and outcome data for other eras studied.

Table S1. Weblinks to code lists for each of the variables used in the study.

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