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CRP in the first 30 postoperative days and its discriminative value as a marker for postoperative infections.

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Abstract

Objective: To assess the association of CRP with postoperative infections for all types of surgery using big data.

Design: A multicenter cohort study with longitudinally collected electronic health records, collected from January 1, 2011, to September 22, 2023.

Setting: Data of two tertiary medical centers in the Netherlands were used.

Participants: This study included all procedures in adult patients undergoing surgery in two tertiary medical centers in the Netherlands. A total of 42,125 surgical procedures from 40,009 unique patients were included.

Outcome measures: The primary outcome was the association between CRP and postoperative infection in the first 30 days postoperatively. Postoperative infection was defined as being treated for an infection with antimicrobial treatment and/or an intervention. CRP measurements were divided into a reference group (0-5.0 mg/dL) and four groups for comparison (5.1-10.0 mg/dL, 10.1-15.0 mg/dL, 15.1-20.0 mg/dL and >20.0 mg/dL). Subgroup analyses were performed for eight major surgical subspecialties and for the two medical centers separately.

Results: A total of 175,779 CRP measurements were performed, of which the majority was drawn in the first postoperative week. Higher CRP levels were associated with higher risk of developing a postoperative infection. The odds ratios (ORs) varied between 1.0 and 12.0, with a stronger association for the higher level of CRP categories and more time elapsed since surgery. For the surgical subspecialties and the two hospitals separately, similar results were found.

Conclusion : In this study, an elevated postoperative CRP was associated with postoperative infections with a stronger association for higher CRP levels. The association was stronger if a longer time elapsed since surgery, which contrasts with the moment most CRP measurements were done,

namely in the first postoperative week. Clinicians should take the evolving value of CRP in mind when using it in the diagnosis of postoperative infections.

Strengths and limitations of this study

- This study included a large number of patients for whom detailed data was available, including 30 days postoperative follow-up, providing us insight in the clinical use and value of CRP in the diagnosis of postoperative infections.
- The operationalized definition for postoperative infections was tested by experts through a manual review of a random sample of patient charts and showed good correspondence.
- A limitation was that for obvious reasons, the exact start of the infection could not be precisely determined. To prevent CRP measurements in patients with a beginning infection being counted in the group of patients without an infection, patients were excluded from the group without postoperative infection one week before start of the infection treatment.

Key words

Postoperative infection, C-reactive protein, Big-data, Diagnostic test

Introduction

More than 300 million surgical procedures are performed worldwide each year[1]. It is estimated that 6.5 to 18 percent of all patients undergoing surgery will develop a postoperative infection in the first 30 postoperative days[2-5]. A large proportion of infections is diagnosed after the eighth postoperative day and increasingly after discharge from the hospital[6,7]. Early diagnosis and treatment are essential to prevent further deterioration of the clinical condition of the patient. Moreover, unnecessary treatment with antibiotics or reintervention should be avoided. A wide array of serum biomarkers and prediction models have been used to discriminate between patients with- and without a postoperative infection. The most widely available and used marker for this purpose is C-reactive protein (CRP).

C-reactive protein is an acute phase protein, constructed from five non-covalently bonded monomeric substructures and produced in the liver in case of inflammation or infection in response to pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α)[8,9]. CRP-levels are elevated during the first postoperative days due to tissue damage caused by the surgery itself, with its peak around the third postoperative day[9,10]. After these first days, CRP slowly declines to its baseline values. Consequently, a high CRP in the first postoperative days often causes a clinical dilemma: it is either a normal postoperative elevated CRP or a first sign of infection. Meta-analyses have shown different discriminative accuracies of CRP in patients undergoing surgery, with a C-statistic varying between 0.66 to 1.00[11-13]. These variations in predictive value may be explained by differences in selected cut-off values, postoperative day of measurement, type of surgery and the type of predicted infection[11-13]. Moreover, most studies have focused on CRP-levels in the first postoperative week, included only a small number of patients and used different diagnostic criteria for postoperative infection. By analyzing the CRP-data from a large multi-center cohort of postoperative patients, with a follow-up of 30 days postoperative and a

standardized definition for a postoperative infection, we aimed to gain insight into the clinical use of CRP and its potential value as a biomarker in the diagnosis of postoperative infections.

Methods

Study design and population

We conducted a cohort study with the use of electronic health record databases as part of the PERISCOPE project [14]. The PERSISCOPE study aims to develop, validate and locally retrain a machine learning algorithm for the prediction of postoperative infections with the use of existing data from electronical health records [14].

These databases include detailed information about 158,703 procedures in adult patients (age ≥18 years) that underwent surgery in two large tertiary medical centers in the Netherlands (the Leiden University Medical Center (LUMC) and the Radboud University Medical Center Nijmegen (RadboudUMC)) between 1-1-2011 and 22-9-2023. See eTable 1 in the Supplement for a full list of data types used from the databases. Procedures from eight surgical subspecialties (general surgery, cardiothoracic surgery, neurosurgery, urological surgery, orthopedic surgery, gynecological surgery, ear-nose-throat (ENT) surgery and maxillofacial surgery) were included. Patients could be included more than once when they underwent multiple surgeries within the period of study. Re-operations within 30 days of the previous surgery were excluded.

As there is under-registration of complications in real-life clinical practice[15], a clinical action-based definition of postoperative infection was used in which postoperative infections were defined as the start of non-prophylactic antibiotics (initiated >24 hours postoperatively and with a minimum duration of 72 hours) and/or a surgical intervention for an infection such as drainage and re-operation within 30 days of the index surgery. All types of postoperative infections were included. See eTable 2 in the Supplement for the full definition used for postoperative infection. All CRP values measured up to 30 days postoperatively were included. Patients without any CRP measurement in the postoperative period or patients with a possible preoperative infection based on the surgical

procedure (manually checked with the use of ICD10 codes and other, hospital specific, diagnosis codes) or a preoperative CRP > 2.5 mg/dL in the five days preceding the operative procedure were excluded from all analyses (n=5343).

Statistical analysis

To analyze the CRP results, patients were divided into two groups based on their infection status for each postoperative week separately. CRP measurements from patients who developed a postoperative infection within 30 days of surgery were included in the group without an infection until one week before developing the postoperative infection, as the precise moment of start of the infection could not be determined retrospectively. In the postoperative infection group only CRP measurements from the 24 hours before and after the start of treatment were included for analyses (eFigure 1 in the Supplement). If multiple CRP values of one patient on the same day were available, the maximum CRP value for that day was used.

Descriptive statistics were used for baseline characteristics. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were reported as absolute numbers and percentages. The Mann Withney U test was used for continuous variables as data was not normally distributed. The Chi Square test was used for categorial variables. Odds ratios (ORs) with 95% confidence intervals (95%CI), sensitivity, specificity and negative and positive predictive values were calculated to examine the strength of the association between postoperative infection and CRP (per stratum: 5.1-10.0 mg/dL, 10.1-15.0 mg/dL, 15.1-20.0 mg/dL and >20.0 mg/dL) per postoperative week. The CRP-range of 0-5.0 mg/dL was used as the reference stratum. A subgroup analysis was performed for the different major surgical subspecialties and for the two hospitals separately. Missing CRP data was not missing at random and was therefore not imputed.

All statistical analyses were performed in Python (Python Software Foundation, Beaverton USA, version 3.8).

Ethics

The study was approved by the Medical Ethics Committee of both participating centers (METC protocol nr G18.129), the research performed with the data complied to the Dutch legislation, the declaration of Helsinki and good clinical practice.

Results

Of the 158,703 procedures in the database, a total of 45,125 surgical procedures from 40,009 unique patients were included in the study. 113,578 procedures were excluded because they were either a re-operation within the 30-day postoperative period, did not have a recorded CRP measurement in the 30-day postoperative period, or because they had an elevated CRP (>2.5 mg/dL) in the preoperative period. During the first 30 days postoperatively, 175,779 CRP measurements were recorded, of which the majority (n = 107,002; 61%) was requested in the first week (Figure 1).

In 9,905 (22%) of the procedures a postoperative infection was present. Postoperative infections occurred more often in male patients and in non-elective procedures. All baseline characteristics of the included procedures are summarized in Table 1. CRP levels in patients with- and without a postoperative infection were almost similar in the first days postoperatively. After the first week, patients with a postoperative infection more often had an elevated CRP and a higher CRP compared to patients without a postoperative infection (Figure 2). The OR for developing a postoperative infection increased with higher CRP category and a longer time elapsed since surgery. The ORs varied between 1.0 (CRP 5.1-10.0 mg/dL in the first postoperative week) and 12.0 (CRP >20.0 mg/dL in the third postoperative week) (Figure 3, Table S4). Sensitivity was low for all weeks and CRP value-categories, ranging between 11% and 34%. Specificity ranged between 64% and 96% and increased with higher CRP categories and a longer time since surgery. The positive predictive value (PPV) of CRP ranged between 12% and 51%. The negative predictive value of a CRP ≤5.0 mg/dL ranged between 88% and 94% (Table S4).

Table 1. Descriptive characteristics of included surgical procedures

	All procedures (n = 45,125)	**No postoperative infection (n = 35,220)**	**Postoperative infection (n = 9,905)**	**P-value[a]**
Age, y (IQR)	63.0 (52.0-72.0)	63.0 (52.0-72.0)	63.0 (52.0-71.0)	0.395
Male sex, No. (%)	26,120 (57.9)	20,206 (57.4)	5,914 (59.7)	<0.001
Procedure urgency[b]				
Elective procedure, No. (%)	33,042 (73.2)	25,944 (73.7)	7,098 (71.7)	<0.001
Non-elective procedure, No. (%)	7,764 (17.2)	5,280 (15.0)	2,484 (25.1)	
Missing, No. (%)	4,319 (9.6)	3,946 (11.2)	323 (3.3)	
Procedure duration, median (IQR), minutes	176 (95 - 285)	180 (96 - 291)	163 (94 - 262)	<0.001
Type of surgery				
General surgery, No. (%)	14,916 (33.1)	10,420 (29.6)	4,496 (45.4)	<0.001
Cardiothoracic surgery, No. (%)	14,918 (33.1)	13,416 (38.1)	1,502 (15.2)	
Neurosurgery, No. (%)	4,418 (9.8)	3,577 (10.2)	841 (8.5)	
Urological surgery, No. (%)	3,758 (8.3)	2,650 (7.5)	1,108 (11.2)	
Orthopedic surgery, No. (%)	3,031 (6.7)	2,071 (5.9)	960 (9.7)	
Gynecological surgery, No. (%)	2,200 (4.9)	1,786 (5.1)	414 (4.2)	
ENT surgery, No. (%)	1,390 (3.1)	959 (2.7)	431 (4.4)	
Maxillofacial surgery, No. (%)	494 (1.1)	341 (1.0)	153 (1.5)	

Abbreviations: ENT, Ear-, nose and throat; IQR, Interquartile range.

[a]The Mann Withney U test for continuous variables and the Chi Square test for categorial variables.

[b]Procedure urgency as registered in the electronic health record registration.

Surgical subspecialties

Eight different surgical subspecialties were included, i.e., general surgery, cardiothoracic surgery, neurosurgery, urological surgery, orthopedic surgery, gynecological surgery, ENT surgery and maxillofacial surgery. Most CRP measurements were performed after cardiothoracic surgery (90% of the included procedures had at least one CRP measurement in the 30--day postoperative period) and least CRP measurements after maxillofacial surgery (7% of the procedures). In all subspecialties, the association between CRP and postoperative infection was stronger in weeks 2-4 postoperatively as compared to the first week postoperatively (Figure 4). The strength of the association between CRP and postoperative infection differed per surgical subspecialty. Especially in the first postoperative week there was only a small association between CRP and infection in general, cardiothoracic surgery and orthopedic surgery, see eTables 5-12 in the Supplement for all the subgroup analyses results.

Differences between hospitals

Of the 170,791 CRP measurements included, 131,365 (77%) were performed in the LUMC and 39,426 (23%) in the RadboudUMC. In the LUMC there were more patients with a CRP measurement as well as more CRP measurements per patient. This difference was largest in the first week postoperative (eTable 13 in the Supplement). The association between CRP and a postoperative infection in the LUMC and RadboudUMC was similar in both hospitals (eFigure 2 in the Supplement).

Discussion

We found that an elevated postoperative CRP was associated with postoperative infections, with a stronger association for a higher level of CRP and longer time elapsed since surgery, while in contrast, most CRP measurements were done in the first postoperative week. Hence, an imbalance seems to exist between the timeframe in which most CRP measurements are performed and when it has the highest diagnostic value.

The stronger association between postoperative CRP and infection when more time since surgery has elapsed, is in accordance with the normal early postoperative rise and fall of CRP, caused by inflammation by the surgery itself. In addition, patients in the hospital more than one week after their surgery, are more likely to have complications. Consequently, CRP measurements beyond this first week are possibly more based on clinical suspicion compared to the more routinely performed measurements in the first postoperative week. On the other hand, non-infectious postoperative complications such as fluid overload, non-septic shock, thrombosis and hypoxemia can lead to inflammation and an elevated CRP [16-19]. Altogether, our results show a strong correlation between CRP and infection. In combination with clinical evaluation and additional diagnostic tests, postoperative CRP can aid to diagnose or rule out a postoperative infection.

Besides CRP, other biomarkers like procalcitonin have been studied for their use in the diagnosis of postoperative infections. Procalcitonin levels increase in response to bacterial infection or sepsis, and are considered to be more specific for bacterial infection than CRP[11,20]. However, for the purpose of diagnosing postoperative infections, procalcitonin has only been studied in small cohorts with conflicting results. In a meta-analysis in cardiac surgery patients, a mean sensitivity of 0.67 (0.47-0.82), and mean specificity of 0.73 (0.65-0.79) were found with a PPV around 50% and a NPV of >90%[21]. This is similar to two other meta-analysis in gastro-intestinal and pancreatic surgery[11,20]. In general, procalcitonin seems to be insufficiently specific for the diagnosis of postoperative infections, although it has a good NPV and could therefore be useful to exclude a postoperative infection when procalcitonin is low. This concurs with our results on CRP. Because we included only observational data and procalcitonin was not routinely measured, no comparison could be made between procalcitonin and CRP. Other biomarkers that have been evaluated as markers for postoperative infections include IL6, IL18, white cell count, neutrophils, lactate and surface receptor CD64[20,22-24]. These studies show that none of these biomarkers was able to diagnose a postoperative infection with a high accuracy.

Between the eight different surgical subspecialties notable differences were observed regarding the association between CRP and postoperative infection. The odd ratios were lowest in the first postoperative week for general surgery, cardiothoracic surgery, and orthopedic surgery (ranging between 1.0 and 5.5). Potentially, larger wound-beds are created in these types of surgical interventions that in turn cause a more extensive postoperative inflammatory reaction. In contrary to ENT, maxillofacial surgery and gynecology which had the highest odd ratios in the first postoperative week (ranging between 2.4 and 19.9).

Fewer postoperative CRP measurements per patient were performed in the RadboudUMC compared to the LUMC. Several factors could account for this difference such as variations in protocols regarding postoperative laboratory ordering, use of change in CRP instead of single CRP values in the diagnosis of infection, or the use of CRP to monitor treatment. Even though the number of CRP measurements differed, the association between CRP and postoperative infections was similar, with a stronger association from the second postoperative week onwards.

This study included a high number of procedures and observational CRP measurements and comprised multiple types of surgery as well as a follow-up time of 30 days. Many previous investigations on the relationship between CRP and postoperative infections included only one surgical subspecialty, fewer procedures and had a shorter follow-up. For example, the meta-analysis of Yeung et al.[12] focuses on colorectal surgery, had a total of 6,647 patients from 23 studies included, and had a follow-up of seven days postoperative. In comparison, our study has electronic health care data from 42,125 procedures, providing insight into the clinical use of CRP and the value of CRP as used in clinical practice.

Limitations

Several limitations of this study need to be considered. The use of a large electronic health record database - i.e., 'big data' – made it impossible to verify every infection by manual chart review. Therefore, an action-based definition of infection was used and defined by the start of non-prophylactic antibiotics with a duration of at least 72h and/or an infection-related surgical re-

intervention. Importantly, for a random sample of patients (n=100), manual chart review was performed and showed good correspondence between the action-based definition and diagnosis of postoperative infection by experts. It is still possible that patients without a postoperative infection have had antibiotics or a re-intervention and that this was done (partly) based on an elevated CRP. However, the Netherlands has a high standard of antibiotic stewardship and manual labeling has other limitations, e.g., interobserver variability and error rates. A second limitation is that the exact start of an infection could not be determined, but this is always difficult if not impossible. As a practical approach to this dilemma, patients were excluded from the group without a postoperative infection one week before start of infection treatment to avoid CRP measurements in patients with a beginning infection being counted in the group of patients without an infection. Lastly, we excluded patients with a preoperative CRP >2.5 mg/dL to prevent patients with a preoperative infection from being classified as having a postoperative infection. Cole et al.[9] previously showed that about 5% of the patients have a preoperative CRP >3.0 mg/dL which was probably related to comorbidities. Possibly, we have excluded patients with an elevated CRP due to comorbidities instead of preoperative infection. For this study, the inclusion of patients with a preoperative infection would be of greater impact than the exclusion of a patient with an elevated CRP due to comorbidities. In addition, not every patient had a preoperative CRP measured. Therefore, patients with an unknown elevated CRP could have been included in the study. Seemingly, these patients had no reason for measuring a preoperative CRP, making a preoperative infection much less likely. The study of Cole et al. did not show a difference in CRP between patients with- and without an infection in the first postoperative week, irrespective of the preoperative CRP, which agrees with the results of this study.

Summary and Conclusions

This study revealed that the association between CRP levels and postoperative infections is dependent of the CRP level, the time elapsed since surgery and the surgical subspecialty. Currently, CRP assessments are performed within the initial week after surgery, despite their limited clinical

significance. Clinicians need to recognize the evolving nature of postoperative CRP values for the diagnosis of postoperative infections and advance to more selective and consciously performed CRP assessments to optimally utilize its diagnostic capacities. Moreover, these results elucidate the difficulty of using CRP in clinical prediction models and are therefore highly significant for the development of new clinical prediction models incorporating CRP.

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Competing interest statement

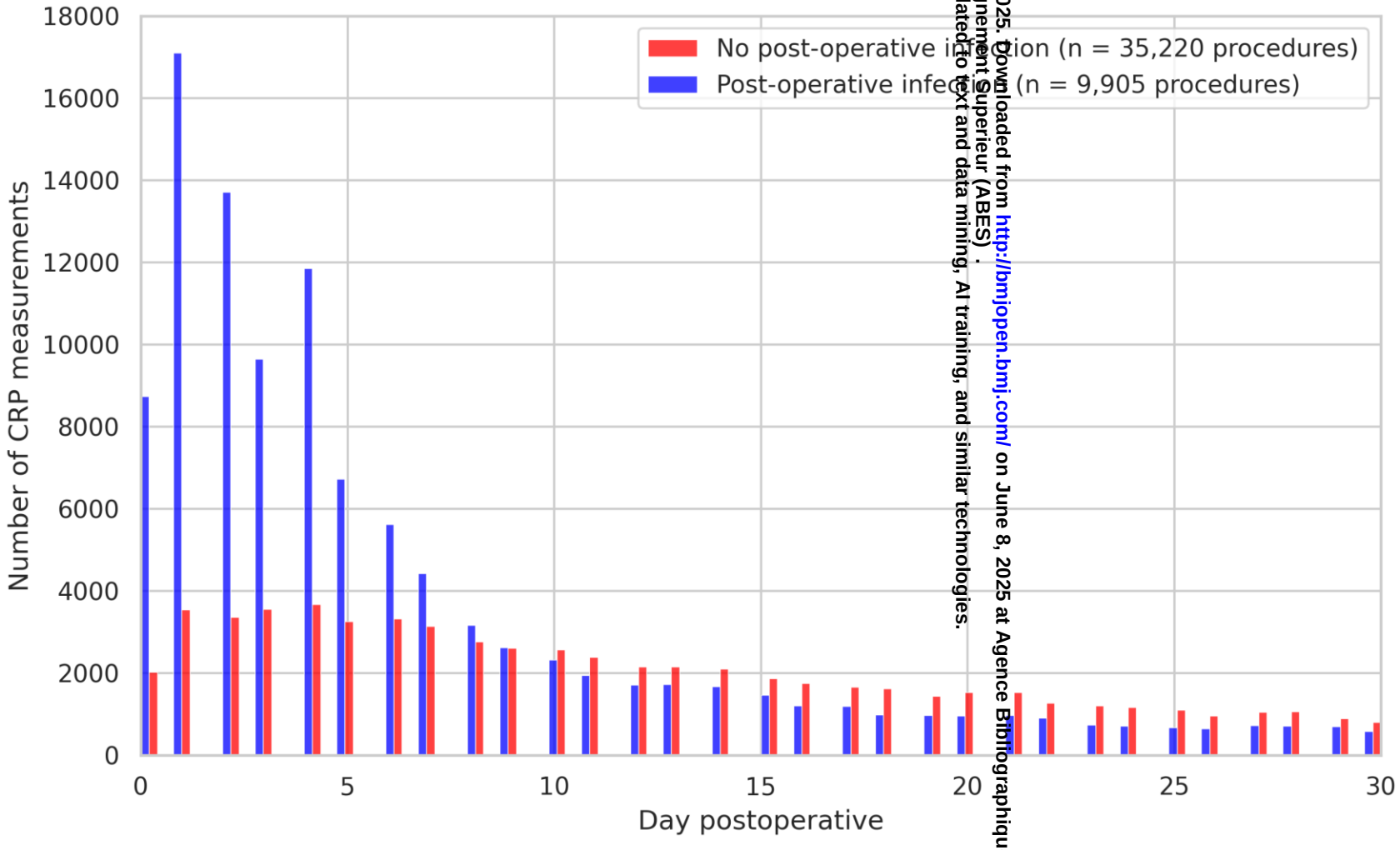
BG is currently CEO and majority shareholder of Healthplus.ai B.V. and subsidiaries. SvdM works as a data scientist and PhD at Healthplus.ai and LUMC. SvdM owns share options in Healthplus.ai.

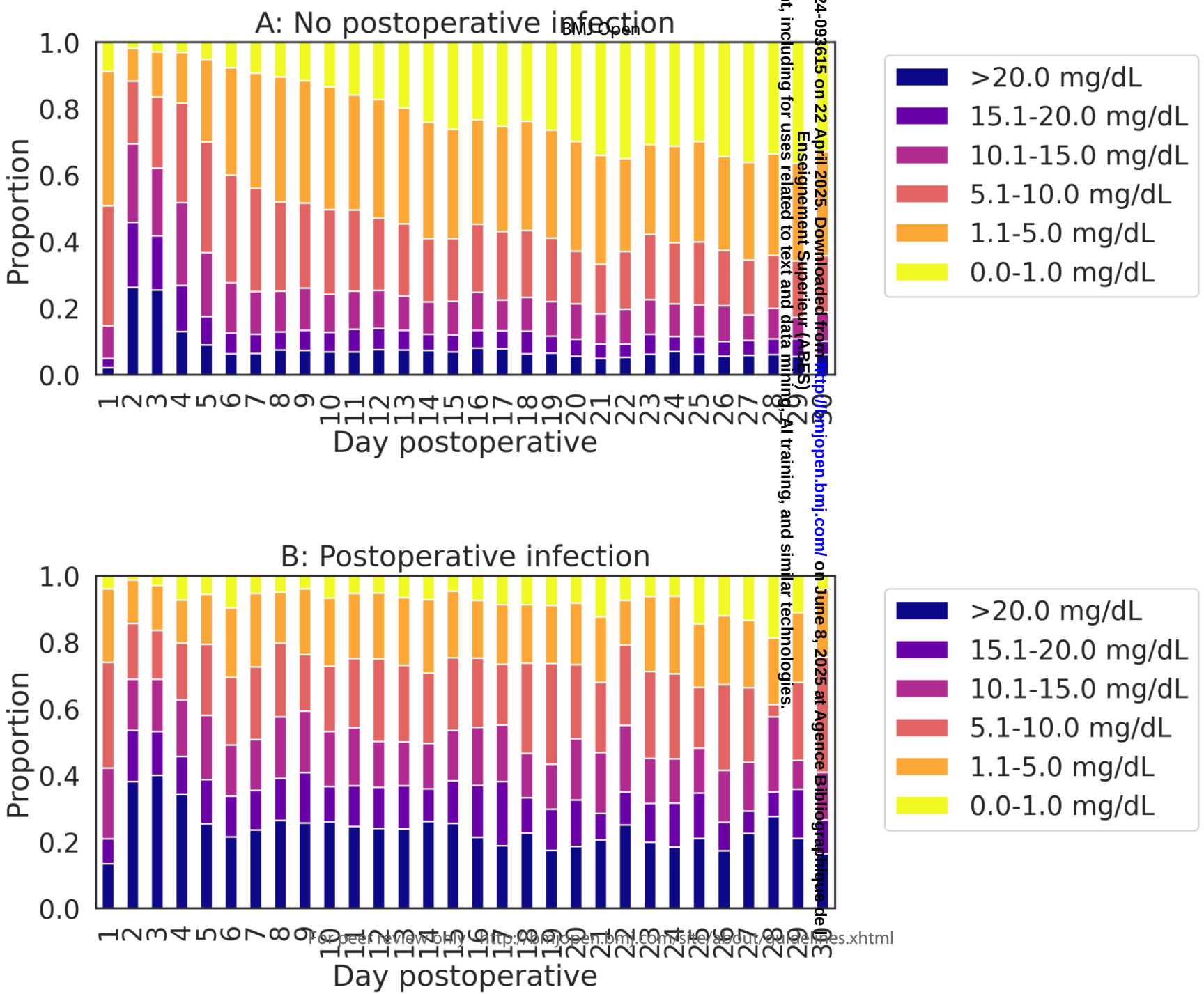
Contributors:

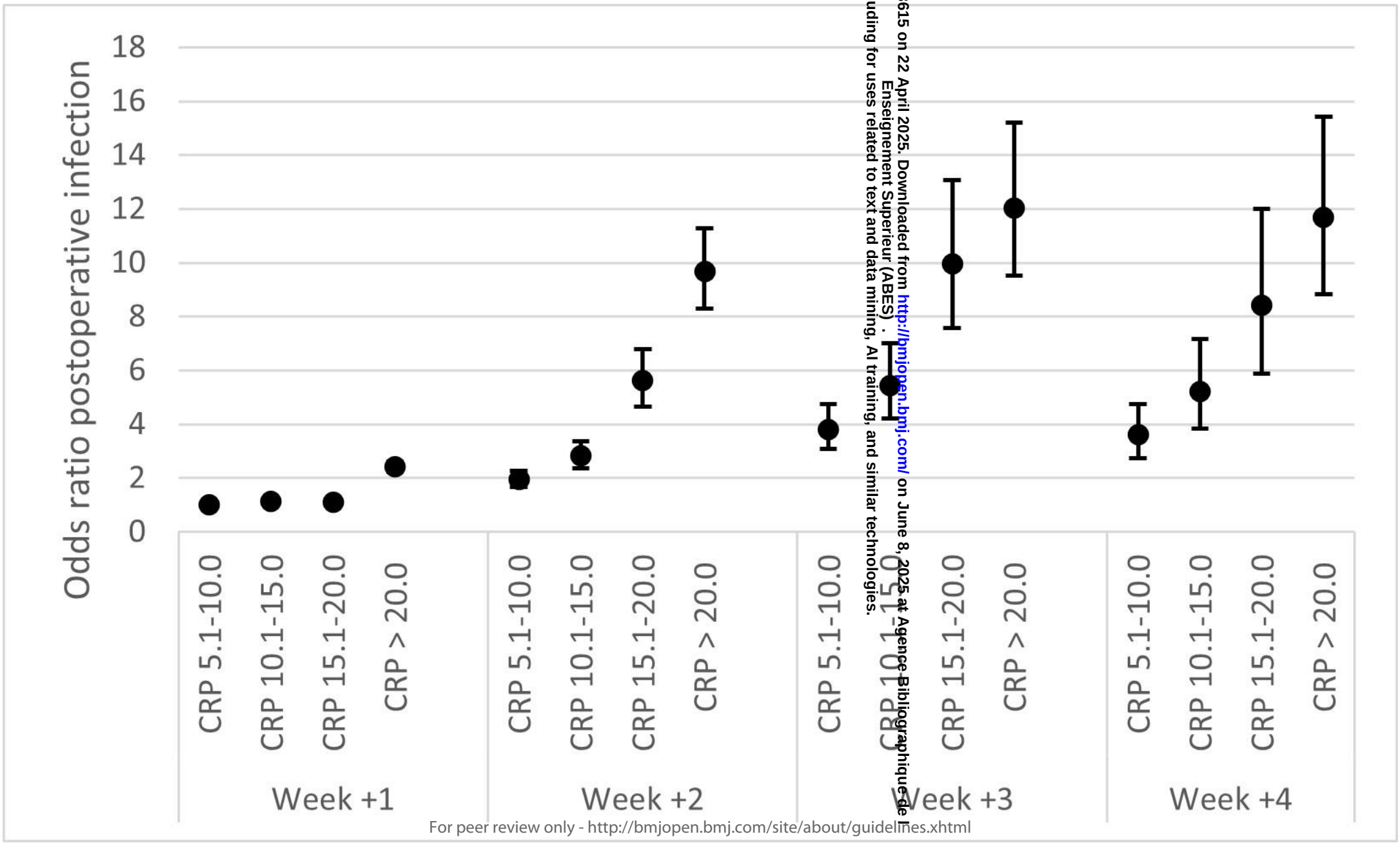
AB: methodology, analysis, writing original draft. SM: methodology, analysis, data-collection, writing-review and editing. BG: data-collection, writing-review and editing, conceptualization. HG: writing-review and editing, conceptualization. NG: methodology, writing-review and editing. SA: writing-review and editing, conceptualization, supervision. MB: writing-review and editing, conceptualization, supervision. The periscope study group: data-collection, conceptualization, writing-review and editing.

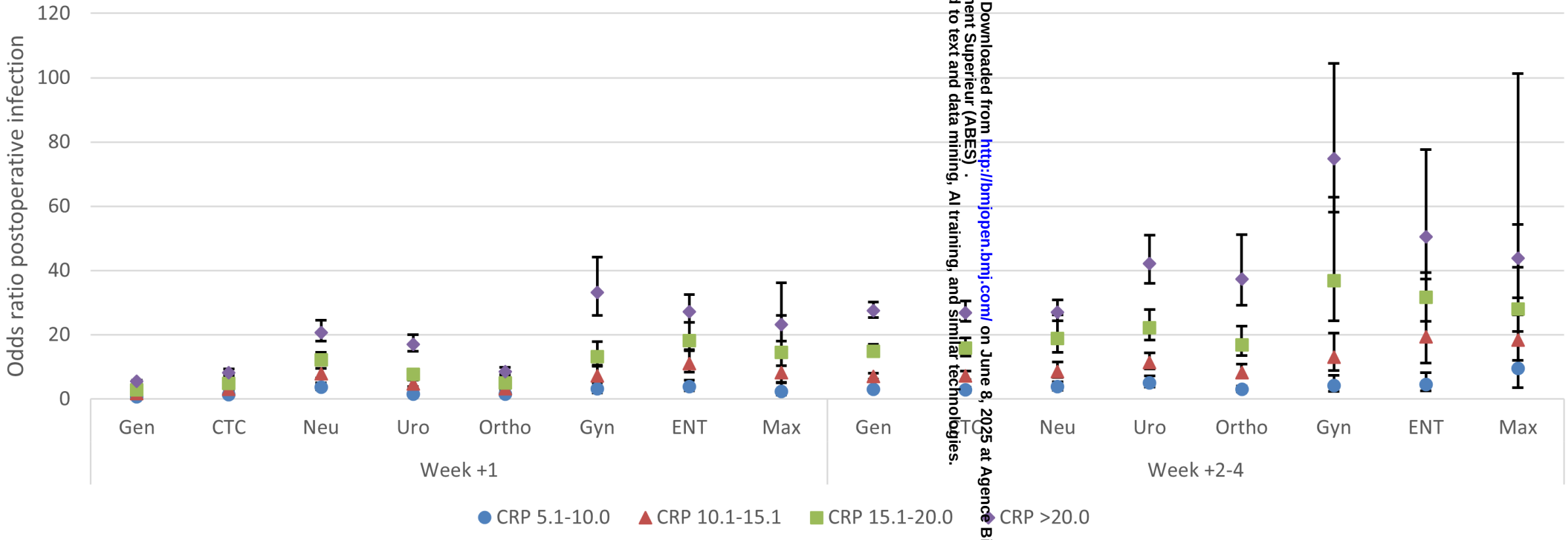
Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Data sharing statement: Data are available upon reasonable request.





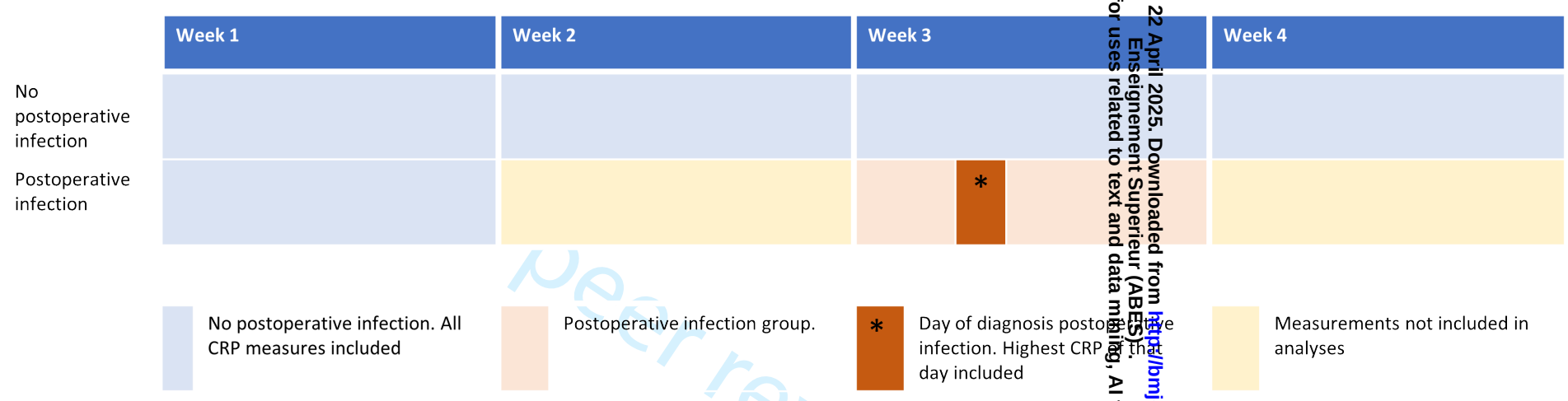




Supplemental Online Content

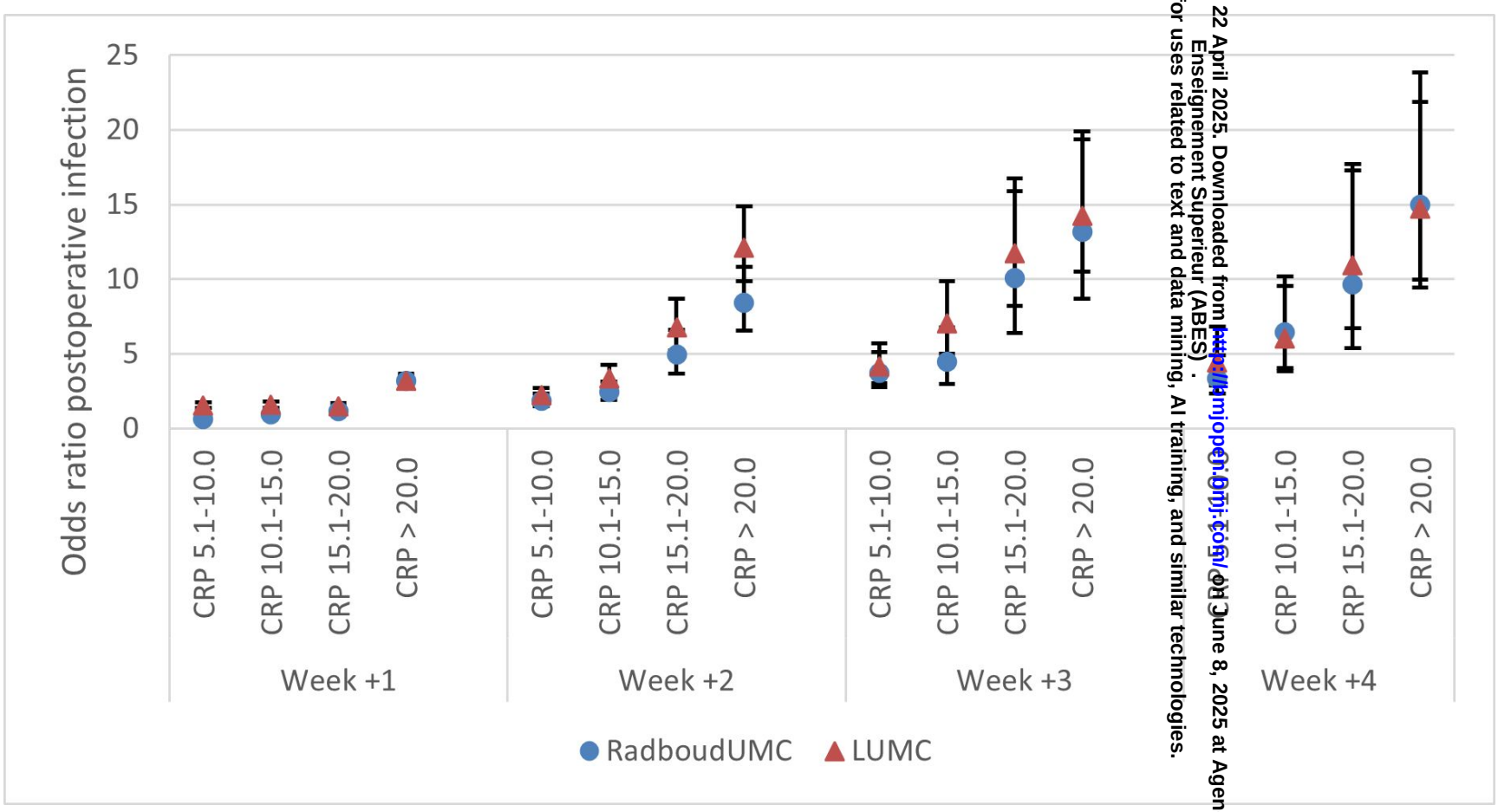
van Boekel AM, van der Meijden SL, Geerts BF, et al. CRP in the first 30 postoperative days and its discriminative value as a marker for postoperative infections.

eFigure 1. Inclusion of CRP measurements of patients with- and without a postoperative infection.



Legend eFigure 1. In this example, a patient developed a postoperative infection in week 3. Therefore, measurements from week 1 were included in the 'No postoperative infection' group, measurements from week 2 and 4 were excluded, and measurements 24 hours before and after the start of therapy in week 3 were included in the 'Postoperative infection' group.

eFigure 2. Odds ratios for the different CRP groups per week postoperative per hospital.



Legend eFigure 2. Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 5.1-10.0 mg/dL was taken as a reference. Black bars denote 95% confidence intervals. CRP is reported in mg/dL, to convert to mg/L multiply values by 10.

eTable 1. Data extracted from the electronic health record

General surgery and anesthesia information	Local used ID of surgery, description of primary diagnosis, date of surgery, international or national codes for surgery and diagnosis if present (for instance ICD9 or 10), date of diagnosis, date and time of admission, date and time of discharge, admission type (elective/non-elective/day), specialty, location, procedure urgency.
Complications	Complication registration of infectious complications (surgical site infections, pneumonia, urinary tract infection, sepsis, etc.).
Medication	Home medication prescriptions (product name, quantity per day, preferable (local, national or international medication code, like ATC), hospital prescribed medication and administration (Start, Stop date and time, quantity and route of administration).
Laboratory and microbiology results	Chemistry, hematology, blood bank, cultures and stains
Patient data	Age, gender, weight, length, open text on past medical history and procedures (anesthesia pre-assessment field most often) and all anesthesia and surgery questionnaires (incl. operator, time and date).

eTable 2. Infection definition used to identify patients with a postoperative infection within 30 days of surgery

#	Criterion	Condition	Explanation
1	Infection treated with antibiotics	Patient received antibiotic treatment between >= 24 hours and <= 30 days after surgery, with a duration longer than 3 days. BUT NOT extended (beyond 24 hours after surgery) prophylaxis and non-infection related regimens[a]	Infections are treated with antibiotics (ATC codes starting with J01). Some patients (depending on surgery type and patient history) will receive prophylactic antibiotics in the period before, or directly after surgery. To exclude prophylactic antibiotics, treatment has to start after >= 24 h after surgery. Other specific (gastro-intestinal and asplenic) prophylactic regimes are excluded as well. Some patients will receive gastroparesis treatment in the form of erythromycin, which is not to treat a bacterial infection. Sometimes, an infection is suspected for which antibiotics is started, but cultures may come back negative. To exclude these cases, the minimum duration is set at 3 days.
AND/OR			
2	Infection treated with surgical intervention	Patient received a surgical intervention related to treatment of infection within 0 days < surgery < 30 days BUT NOT during initial surgery itself.	(Deep) surgical site infections sometimes require repeated surgery to drain the infection and/or clean the wound. These treatments are done at the operating room and are therefore registered as surgical procedures. The different types of surgical procedures performed at each hospital are filtered on treatments related to postoperative infections.

Abbreviations: ATC code, anatomical therapeutic chemical classification code.

[a]Prophylactic regimes that are excluded are hospital specific. Excluded for this research were:
1. Gastro-intestinal surgery antibiotic prophylaxis; continued on Cefuroxime AND Metronidazole started within 24 hours after surgery up to 5 days. 2. Asplenic patient prophylaxis (1 dd 480 mg Cotrimoxazole (PCP prophylaxis), OR 1 dd 250 mg azithromycin, OR 1 dd 500 mg clarithromycin, OR 1 dd 500mg or 2 dd 250mg amoxicillin (500mg per day in total), OR 1dd 500mg or 2dd 250mg pheneticillin) (500mg per day in total)). 3. Gastroparesis treatment (Low-dose (100 mg) erythromycin)

eTable 3. Descriptive characteristics of included procedures per hospital

	All procedures (n = 45,125)	LUMC (n = 29,136)	RadboudUMC (n = 15,989)	P-value[a]
Age, y (IQR)	63.0 (52.0-72.0)	63.0 (52.0-72.0)	63.0 (52.0-71.0)	0.019
Male sex, No. (%)	26,120 (57.9)	16,829 (57.8)	9,291 (58.1)	0.479
Procedure urgency[b]				
Elective procedure, No. (%)	33,042 (73.2)	19,810 (68.0)	13,232 (82.8)	<0.001
Non-elective procedure, No. (%)	7,764 (17.2)	5,007 (17.2)	2,757 (17,2)	
Missing, No. (%)	4,319 (9.6)	4,319 (14,8)	0 (0)	
Procedure duration, median (IQR), minutes	176 (95 - 285)	198 (106 - 319)	151 (78 - 222)	<0.001
Type of surgery				
General surgery, No. (%)	14,916 (33.1)	10,929 (37.5)	3,987 (24.9)	<0.001
Cardiothoracic surgery, No. (%)	14,918 (33.1)	10,498 (36.0)	4,420 (27.6)	
Neurosurgery, No. (%)	4,418 (9.8)	3,014 (10.3)	1,404 (8.8)	
Urological surgery, No. (%)	3,758 (8.3)	1,096 (3.8)	2,662 (16.6)	
Orthopedic surgery, No. (%)	3,031 (6.7)	1,338 (4.6)	1,693 (10.6)	
Gynecological surgery, No. (%)	2,200 (4.9)	1,078 (3.7)	1,122 (7.0)	
ENT surgery, No. (%)	1,390 (3.1)	1,018 (3.5)	372 (2.3)	
Maxillofacial surgery, No. (%)	494 (1.1)	165 (0.6)	329 (2.1)	

Abbreviations: ENT, Ear-, nose and throat; IQR, Interquartile range.

[a]The Mann Withney U test for continuous variables and the Chi Square test for categorial variables.

[b]Procedure urgency as registered in the electronic health record registration.

eTable 4. Comparison of CRP values[a] in patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	1,458	10,346					
Week +2	476	4,404					
Week +3	223	3,058					
Week +4[b]	170	2,760					
CRP 5.1-10.0 mg/dL							
Week +1	817	5,785	1.0 (0.91-1.1)	14.7	64.1	12.4	87.6
Week +2	355	1,690	1.94 (1.67-2.25)	19.4	72.3	17.4	90.2
Week +3	175	630	3.81 (3.07-4.73)	21.1	82.9	21,7	93.2
Week +4[b]	89	401	3.6 (2.73-4.75)	17.5	87.3	18.2	94.2
CRP 10.1-15.0 mg/dL							
Week +1	797	4,992	1.13 (1.03-1.24)	14.4	67.5	13.8	87.6
Week +2	`235	771	2.82 (2.37-3.36)	12.8	85.1	23.4	90.2
Week +3	115	290	5.44 (4.21-7.02)	13.8	91.3	28.4	93.2
Week +4[b]	69	214	5.23 (3.83-7.15)	13.6	92.8	24.4	94.2
CRP 15.1-20.0 mg/dL							
Week +1	587	3,796	1.1 (0.99-1.22)	10.6	73.2	13.4	87.6
Week +2	232	382	5.62 (4.65-6.79)	12.7	92	37.8	90.2
Week +3	119	164	9.95 (7.58-13.0)	14.3	94.9	42	93.2
Week +4[b]	57	110	8.41 (5.89-12.0)	11.2	96.2	34.1	94.2
CRP >20.0 mg/dL							
Week +1	1,893	5,551	2.42 (2.24-2.61)	34.1	65.1	25.4	87.6

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP >20.0 mg/dL							
Week +2	531	508	9.67 (8.29-11.2)	29	89.7	51.1	90.2
Week +3	199	227	12.02 (9.51-15.1)	23.9	93.1	46.7	93.2
Week +4[b]	123	171	11.68 (8.84-15.4)	24.2	94.2	41.8	94.2

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 5. Comparison of CRP values[a] in general surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	870	3,459					
Week +2-4[b]	314	3,151					
CRP 5.1-10.0 mg/dL							
Week +1	343	1,912	0.71 (0.62-0.81)	12.1	64.4	15.2	79.9
Week +2-4[b]	215	730	2.96 (2.44-3.58)	17.8	81.2	22.8	90.9
CRP 10.1-15.0 mg/dL							
Week +1	351	1,373	1.02 (0.89-1.17)	12.4	71.6	20.4	79.9
Week +2-4[b]	145	359	4.05 (3.23-5.07)	12	89.8	28.8	90.9
CRP 15.1-20.0 mg/dL							
Week +1	268	946	1.13 (0.97-1.32)	9.5	78.5	22.1	79.9
Week +2-4[b]	158	201	7.89 (6.22-10.02)	13.1	94	44	90.9
CRP >20.0 mg/dL		297					
Week +1	997	1,489	2.66 (2.38-2.97)	35.2	69.9	40.1	79.9
Week +2-4[b]	375		12.67 (10.46-15.34)	31.1	91.4	55.8	90.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 6. Comparison of CRP values[a] in cardiothoracic surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	51	1,623					
Week +2-4[b]	88	2,739					
CRP 5.1-10.0 mg/dL							
Week +1	104	2,440	1.36 (0.97-1.91)	12.8	39.9	4.1	97
Week +2-4[b]	117	1,311	2.78 (2.09-3.69)	22.1	67.6	8.2	96.9
CRP 10.1-15.0 mg/dL							
Week +1	150	2,853	1.67 (1.21-2.31)	18.5	36.3	5	97
Week +2-4[b]	88	629	4.35 (3.2-5.92)	16.6	81.3	12.3	96.9
CRP 15.1-20.0 mg/dL							
Week +1	136	2,383	1.82 (1.31-2.53	16.7	40.5	5.4	97
Week +2-4[b]	86	309	8.66 (6.29-11.92)	16.3	89.9	21.8	96.9
CRP >20.0 mg/dL							
Week +1	371	3,508	3.37 (2.5-4.54)	45.7	31.6	9.6	97
Week +2-4[b]	150	420	11.12 (8.38-14.75)	28.4	86.7	26.3	96.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 7. Comparison of CRP values[a] in neurosurgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	168	2,295					
Week +2-4[b]	144	1,102					
CRP 5.1-10.0 mg/dL							
Week +1	88	321	3.74 (2.82-4.96)	22.7	87.7	21.5	93.2
Week +2-4[b]	70	142	3.77 (2.7-5.27)	20.3	88.6	33	88.4
CRP 10.1-15.0 mg/dL							
Week +1	46	155	4.05 (2.81-5.83)	11.9	93.7	22.9	93.2
Week +2-4[b]	31	50	4.74 (2.93-7.66)	9	95.7	38.3	88.4
CRP 15.1-20.0 mg/dL							
Week +1	30	95	4.31 (2.78-6.69)	7.7	96	24	93.2
Week +2-4[b]	35	26	10.3 (6.02-17.61)	10.1	97.7	57.4	88.4
CRP >20.0 mg/dL							
Week +1	56	89	8.6 (5.95-12.44)	14.4	96.3	38.6	93.2
Week +2-4[b]	65	61	8.15 (5.52-12.04)	18.8	94.8	51.6	88.4

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 8. Comparison of CRP values[a] in urology patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	115	955					
Week +2-4[b]	94	1,062					
CRP 5.1-10.0 mg/dL							
Week +1	68	390	1.45 (1.05-2.0)	12.5	71	14.8	89.3
Week +2-4[b]	78	174	5.06 (3.6-7.11)	19.3	85.9	31	91.9
CRP 10.1-15.0 mg/dL							
Week +1	94	243	3.21 (2.36-4.36)	17.2	79.7	27.9	89.3
Week +2-4[b]	59	105	6.35 (4.33-9.31)	14.6	91	36	91.9
CRP 15.1-20.0 mg/dL							
Week +1	56	156	2.98 (2.08-4.28)	10.3	86	26.4	89.3
Week +2-4[b]	53	56	10.69 (6.95-16.45)	13.1	95	48.6	91.9
CRP >20.0 mg/dL							
Week +1	213	188	9.41 (7.14-12.39)	39	83.6	53.1	89.3
Week +2-4[b]	121	68	20.1 (13.96-28.93)	29.9	94	64	91.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 9. Comparison of CRP values[a] in orthopedic surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	141	645					
Week +2-4[b]	150	1,088					
CRP 5.1-10.0 mg/dL							
Week +1	100	308	1.49 (1.11-1.99)	22.8	67.7	24.5	82.1
Week +2-4[b]	78	192	2.95 (2.16-4.04)	20.6	85	28.9	87.9
CRP 10.1-15.0 mg/dL							
Week +1	60	162	1.69 (1.19-2.39)	13.7	79.9	27	82.1
Week +2-4[b]	52	71	5.31 (3.57-7.89)	13.7	93.9	42.3	87.9
CRP 15.1-20.0 mg/dL							
Week +1	40	101	1.81 (1.2-2.72)	9.1	86.5	28.4	82.1
Week +2-4[b]	37	31	8.66 (5.22-14.38)	9.8	97.2	54.4	87.9
CRP >20.0 mg/dL							
Week +1	97	126	3.52 (2.55-4.85)	22.1	83.7	43.4	82.1
Week +2-4[b]	62	22	20.44 (12.21-34.23)	16.4	98	73.8	87.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 10. Comparison of CRP values[a] in gynecological surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	38	832					
Week +2-4[b]	35	545					
CRP 5.1-10.0 mg/dL							
Week +1	35	246	3.12 (1.93-5.05)	`17.6	77.2	12.5	95.6
Week +2-4[b]	24	90	4.15 (2.36-7.3)	14.5	85.8	21.1	94
CRP 10.1-15.0 mg/dL							
Week +1	24	129	4.07 (2.36-7.01)	12.1	86.6	15.7	95.6
Week +2-4[b]	22	39	8.78 (4.7-16.39)	13.3	93.3	36.1	94
CRP 15.1-20.0 mg/dL							
Week +1	21	77	5.97 (3.34-10.68)	10.6	91.5	21.4	95.6
Week +2-4[b]	23	12	23.88 (11.45-49.79)	12.9	97.3	60.5	94
CRP >20.0 mg/dL							
Week +1	81	89	19.93 (12.8-31.04)	40.7	90.3	47.6	95.6
Week +2-4[b]	61	25	37.99 (21.32-67.68)	37	95.6	70.9	94

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 11. Comparison of CRP values[a] in ear-, nose- and throat surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	61	430					
Week +2-4[b]	35	394					
CRP 5.1-10.0 mg/dL							
Week +1	61	111	3.87 (2.56-5.84)	23.1	79.5	35.5	87.6
Week +2-4[b]	26	64	4.57 (2.58-8.1)	25	86	28.9	91.8
CRP 10.1-15.0 mg/dL							
Week +1	53	52	7.18 (4.5-11.46)	20.1	89.2	50.5	87.6
Week +2-4[b]	17	13	14.72 (6.61-32.78)	16.3	96.8	56.7	91.8
CRP 15.1-20.0 mg/dL							
Week +1	27	27	7.05 (3.88-12.81)	10.2	84.1	50	87.6
Week +2-4[b]	11	10	12.38 (4.92-31.17)	10.6	97.5	52.4	91.8
CRP >20.0 mg/dL							
Week +1	62	48	9.11 (5.74-14.47)	23.5	90	56.4	87.6
Week +2-4[b]	15	9	18.76 (7.66-45.95)	24.4	97.8	62.5	91.8

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10..

eTable 12. Comparison of CRP values[a] in maxillofacial surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	14	107					
Week +2-4[b]	9	141					
CRP 5.1-10.0 mg/dL							
Week +1	18	57	2.41 (1.12-5.2)	23.7	65.2	24	88.4
Week +2-4[b]	11	18	9.57 (3.49-26.23)	32.4	88.7	37.9	94
CRP 10.1-15.0 mg/dL							
Week +1	19	25	5.81 (2.57-13.14)	25	81.1	43.2	88.4
Week +2-4	5	9	8.7 (2.41-31.42)	14.7	94	35.7	94
CRP 15.1-20.0 mg/dL							
Week +1	9	11	6.25 (2.2-17.72)	11.8	90.7	45	88.4
Week +2-4[b]	5	8	9.79 (2.66-36.1)	14.7	94.6	38.5	94
CRP >20.0 mg/dL							
Week +1	16	14	8.73 (3.52-21.65)	21.1	88.4	53.3	88.4
Week +2-4[b]	4	4	15.67 (3.36-73.17)	11.8	97.2	50	94

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 13. Number of CRP measurements in the LUMC and RadboudUMC

Postoperative week	Patients with CRP measurement	CRP measurements	Measurements per procedure[a]	Average measurements[b]
LUMC				
1	23,914	83,552	3.5	0.28
2	7,983	23,027	2.9	0.09
3	4,934	13,655	2.8	0.06
4	3,919	11,131	2.8	0.05
RadboudUMC				
1	10,954	20,155	1.8	0.14
2	4,856	8,906	1.8	0.06
3	3,364	5,532	1.6	0.04
4	2,919	4,833	1.7	0.04

Abbreviations: CPR, C-reactive protein; LUMC, Leiden University Medical Center.

[a]Average CRP measurements per patient in patients with at least one CRP measurement

[b]Average CRP measurements per procedure (Total procedures LUMC 85,269; total procedures RadboudUMC 77,380)

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

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C-reactive protein in the first 30 postoperative days and its discriminative value as a marker for postoperative infections, a multi-center cohort study

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C-reactive protein in the first 30 postoperative days and its discriminative value as a marker for postoperative infections, a multi-center cohort study

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Abstract

Objective: To assess the association of c-reactive protein (CRP) with postoperative infections for eight different types of surgery using big data.

Design: A multicenter cohort study with longitudinally collected data from electronic health records, collected from January 1, 2011, to September 22, 2023.

Setting: Data of two tertiary medical centers in the Netherlands were used.

Participants: This study included all procedures (42,125 in total) in adult patients undergoing surgery in two tertiary medical centers in the Netherlands.

Outcome measures: The primary outcome was the association between CRP and a postoperative infection in the first 30 days postoperatively. Postoperative infection was defined by an action-based definition, i.e. patients had to be treated for an infection with antimicrobial treatment and/or an intervention (e.g. surgical drainage) to be classified as having a postoperative infection. CRP measurements were divided into a reference group (0-5.0 mg/dL) and four groups for comparison (5.1-10.0 mg/dL, 10.1-15.0 mg/dL, 15.1-20.0 mg/dL and >20.0 mg/dL). Subgroup analyses were performed for eight major surgical subspecialties and for the two medical centers separately.

Results: A total of 175,779 CRP measurements were performed, of which the majority was drawn in the first postoperative week. The odds ratios (ORs) for developing a postoperative infection varied between 1.0 (0.9-1.1 95%CI) and 12.0 (9.5-15.1 95%CI), with a stronger association for the higher level of CRP categories and when more time had elapsed since surgery. Sensitivity ranged between 11% and 34%, specificity ranged between 64 and 95%, the positive- and negative predicting value ranged between 12% and 51%, and 88% and 94% respectively. For the surgical subspecialties and the two hospitals separately, similar results were found.

Conclusion : In this study, an elevated postoperative CRP was associated with postoperative infections with a stronger association for higher CRP levels. The association was stronger if a longer

time had elapsed since surgery, which contrasts with the moment most CRP measurements were done, namely in the first postoperative week. Clinicians should take the evolving value of CRP in mind when using it in the diagnosis of postoperative infections.

Strengths and limitations of this study

- The cohort consisted of a large, 'real world' sample of adults from two different academic hospitals.
- A clinical action based definition for postoperative infection was used and tested on a random sample of patients with good correspondence.
- To prevent CRP measurements in patients with a beginning infection being counted in the non-infection group, patients were excluded from the non-infection group one week before start of infection treatment, as the exact start of infection could not precisely be determined.

Key words

Postoperative infection, C-reactive protein, Big-data, Diagnostic test

Introduction

More than 300 million surgical procedures are performed worldwide each year[1]. It is estimated that 6.5 to 18 percent of all patients undergoing surgery will develop a postoperative infection in the first 30 postoperative days[2-5]. A large proportion of infections is diagnosed after the eighth postoperative day and increasingly after discharge from the hospital[6,7]. Early diagnosis and treatment are essential to prevent further deterioration of the clinical condition of the patient. Moreover, unnecessary treatment with antibiotics or a reintervention should be avoided. A wide array of serum biomarkers and prediction models have been used to discriminate between patients with- and without a postoperative infection. The most widely available and used marker for this purpose is C-reactive protein (CRP).

C-reactive protein is an acute phase protein, produced in the liver in case of inflammation or infection in response to pro-inflammatory cytokines[8,9]. CRP levels are elevated during the first. postoperative days due to tissue damage caused by the surgery itself, with its peak around the third postoperative day[9,10]. After these first days, CRP slowly declines to its baseline values. Consequently, a high CRP in the first postoperative days often causes a clinical dilemma: it is either an elevated CRP related to the surgical intervention or a first sign of infection.

This knowledge gap still exists as meta-analyses have shown different discriminative accuracies of CRP in patients who underwent surgery, with a C-statistic varying between 0.66 to 1.00[11-13]. These variations in predictive ability may be explained by differences in selected cut-off values, postoperative day of measurement, type of surgery and the type of predicted infection[11-13]. Moreover, most studies have focused on CRP levels solely in the first postoperative week, included only a small number of patients and used different diagnostic criteria for postoperative infection. Therefore, we have analyzed the CRP-data from a large multi-center cohort of postoperative patients, with a follow-up of 30 days and with the use of a standardized definition for postoperative

infection. The aim of this study was to gain insight into the clinical use of CRP and its potential value as a biomarker in the diagnosis of any type of postoperative infection.

Methods

Study design and population

We conducted a cohort study with the use of electronic health record databases as part of the PERISCOPE project [14]. The PERSISCOPE study aims to develop, validate and locally retrain a machine learning algorithm for the prediction of postoperative infections with the use of existing data from electronical health records [14].

The databases include detailed information about 158,703 procedures in adult patients (age ≥18 years) that underwent surgery in two large tertiary medical centers in the Netherlands (the Leiden University Medical Center (LUMC) and the Radboud University Medical Center Nijmegen (RadboudUMC)) between 1-1-2011 and 22-9-2023. See eTable 1 in the Supplement for a full list of data types used from the databases. Procedures from eight surgical subspecialties (general surgery, cardiothoracic surgery, neurosurgery, urological surgery, orthopedic surgery, gynecological surgery, ear-nose-throat (ENT) surgery and maxillofacial surgery) were included. Patients could be included more than once when they underwent multiple surgeries within the study period. Non-invasive procedures (e.g., anesthesiologic or biopsies) were excluded as well ass, re-operations within 30 days of the previous surgery.

As there is under-registration of complications in real-life clinical practice[15], a clinical action-based definition of postoperative infection was used in which postoperative infections were defined as the start of non-prophylactic antibiotics (initiated >24 hours postoperatively and with a minimum duration of 72 hours) and/or a surgical intervention for an infection such as drainage and re-operation within 30 days of the index surgery. All types of postoperative infections were included. See eTable 2 in the Supplement for the full definition used for postoperative infection. All CRP values measured up to 30 days postoperatively were included. Patients without any CRP measurement in

the postoperative period or patients with a possible preoperative infection based on the surgical procedure (manually checked with the use of ICD10 codes and other, hospital specific, diagnosis codes) or a preoperative CRP > 2.5 mg/dL in the five days preceding the operative procedure were excluded from all analyses.

Statistical analysis

To analyze the CRP results, patients were divided into two groups based on their infection status for each postoperative week separately. CRP measurements from patients who developed a postoperative infection within 30 days of surgery were included in the group without an infection until one week before developing the postoperative infection, as the precise moment of start of the infection could not be determined retrospectively. In the postoperative infection group only CRP measurements from the 24 hours before and after the start of treatment were included for analyses (eFigure 1 in the Supplement). If multiple CRP values of one patient on the same day were available, the maximum CRP value for that day was used.

Descriptive statistics were used for baseline characteristics. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were reported as absolute numbers and percentages. The Mann Withney U test was used for continuous variables as data were not normally distributed. The Chi Square test was used for categorial variables. Odds ratios (ORs) with 95% confidence intervals (95%CI), sensitivity, specificity and negative and positive predictive values were calculated to examine the strength of the association between postoperative infection and CRP (per stratum: 5.1-10.0 mg/dL, 10.1-15.0 mg/dL, 15.1-20.0 mg/dL and >20.0 mg/dL) per postoperative week. The CRP-range of 0-5.0 mg/dL was used as the reference stratum. The stratification of CRP by 5mg/dL was based on consultation of different clinical specialists and clinical expert discussion. A subgroup analysis was performed for the different major surgical subspecialties and for the two hospitals separately. We

judged that most of the time, CRP was measured for a reason, thus, missing CRP data were not missing at random and were therefore not imputed.

All statistical analyses were performed in Python (Python Software Foundation, Beaverton USA, version 3.8).

Ethics

The study was approved by the Medical Ethics Assessment Committee of the LUMC (METC-LDD (Medisch Ethische Toetsingscommissie Leiden-Den Haag-Delft)) and RadboudUMC (METC Oost-Nederland) protocol nr G18.129, the research performed with the data complied to the Dutch legislation, the declaration of Helsinki and good clinical practice. Informed consent was not required as this was a database study with anonymized data.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Of the 158,703 procedures in the database, a total of 45,125 surgical procedures from 40,009 unique patients were included in the study. 113,578 procedures were excluded because they were either a non-invasive procedure (n = 54,461), re-operation within the 30-day postoperative period (n = 12,649), patients did not have a recorded CRP measurement in the 30-day postoperative period (n = 41,125), or because patients had an elevated CRP (>2.5 mg/dL) in the preoperative period (n = 5,343). During the first 30 days postoperatively, 175,779 CRP measurements were recorded, of which the majority (n = 107,002; 61%) was requested in the first week (Figure 1). Lastly, for patients with more than one CRP measurement per day, the maximum value per day was included for the analyses, excluding 4,988 CRP measurements. Therefore, of the 175,779 CRP measurements, 170,791 measurements were included in the final analyses.

In 9,905 (22%) of the procedures a postoperative infection was present. Postoperative infections occurred more often in male patients and in non-elective procedures. All baseline characteristics of the included procedures are summarized in Table 1. CRP levels in patients with- and without a postoperative infection were almost similar in the first days postoperatively. After the first week, patients with a postoperative infection more often had an elevated CRP and a higher CRP compared to patients without a postoperative infection (Figure 2). The OR for developing a postoperative infection increased with higher CRP category and a longer time elapsed since surgery. The ORs varied between 1.0 (CRP 5.1-10.0 mg/dL in the first postoperative week) and 12.0 (CRP >20.0 mg/dL in the third postoperative week) (Figure 3, eTable 3). Sensitivity was low for all weeks and CRP value-categories, ranging between 11% and 34%. Specificity ranged between 64% and 96% and increased with higher CRP categories and a longer time since surgery. The positive predictive value (PPV) of CRP ranged between 12% and 51%. The negative predictive value of a CRP ≤5.0 mg/dL ranged between 88% and 94% (eTable 3).

Table 1. Descriptive characteristics of included surgical procedures

	All procedures (n = 45,125)	**No postoperative infection (n = 35,220)**	**Postoperative infection (n = 9,905)**	**P-value[a]**
Age, y (IQR)	63.0 (52.0-72.0)	63.0 (52.0-72.0)	63.0 (52.0-71.0)	0.395
Male sex, No. (%)	26,120 (57.9)	20,206 (57.4)	5,914 (59.7)	<0.001
Procedure urgency[b]				
Elective procedure, No. (%)	33,042 (73.2)	25,944 (73.7)	7,098 (71.7)	<0.001
Non-elective procedure, No. (%)	7,764 (17.2)	5,280 (15.0)	2,484 (25.1)	
Missing, No. (%)	4,319 (9.6)	3,946 (11.2)	323 (3.3)	
Procedure duration, median (IQR), minutes	176 (95 - 285)	180 (96 - 291)	163 (94 - 262)	<0.001
Type of surgery				

General surgery, No. (%)	14,916 (33.1)	10,420 (29.6)	4,496 (45.4)	<0.001
Cardiothoracic surgery, No. (%)	14,918 (33.1)	13,416 (38.1)	1,502 (15.2)	
Neurosurgery, No. (%)	4,418 (9.8)	3,577 (10.2)	841 (8.5)	
Urological surgery, No. (%)	3,758 (8.3)	2,650 (7.5)	1,108 (11.2)	
Orthopedic surgery, No. (%)	3,031 (6.7)	2,071 (5.9)	960 (9.7)	
Gynecological surgery, No. (%)	2,200 (4.9)	1,786 (5.1)	414 (4.2)	
ENT surgery, No. (%)	1,390 (3.1)	959 (2.7)	431 (4.4)	
Maxillofacial surgery, No. (%)	494 (1.1)	341 (1.0)	153 (1.5)	

Abbreviations: ENT, Ear-, nose and throat; IQR, Interquartile range.

[a]The Mann Withney U test for continuous variables and the Chi Square test for categorial variables.

[b]Procedure urgency as registered in the electronic health record registration.

Surgical subspecialties

Eight different surgical subspecialties were included, i.e., general surgery, cardiothoracic surgery, neurosurgery, urological surgery, orthopedic surgery, gynecological surgery, ENT surgery and maxillofacial surgery. Most CRP measurements were performed after cardiothoracic surgery (90% of the included procedures had at least one CRP measurement in the 30--day postoperative period) and least CRP measurements after maxillofacial surgery (7% of the procedures). In all subspecialties, the association between CRP and postoperative infection was stronger in weeks 2-4 postoperatively as compared to the first week postoperatively (Figure 4). The strength of the association between CRP and postoperative infection differed per surgical subspecialty. Especially in the first postoperative week there was only a small association between CRP and infection in general, cardiothoracic surgery and orthopedic surgery, see eTables 4-11 in the Supplement for all the subgroup analyses results.

Differences between hospitals

Of the 170,791 CRP measurements included, 131,365 (77%) were performed in the LUMC and 39,426 (23%) in the RadboudUMC, see eTable 12 for the descriptive characteristics of the included procedures per hospital. In the LUMC there were more patients with a CRP measurement as well as more CRP measurements per patient. This difference was largest in the first postoperative week (eTable 13 in the Supplement). The association between CRP and a postoperative infection in the LUMC and RadboudUMC was similar in both hospitals (eFigure 2 in the Supplement).

Discussion

We found that an elevated postoperative CRP was associated with postoperative infections, with a stronger association for a higher level of CRP and longer time elapsed since surgery, while in contrast, most CRP measurements were done in the first postoperative week. Hence, an imbalance seems to exist between the timeframe in which most CRP measurements are performed and when it has the highest diagnostic value.

The stronger association between postoperative CRP and infection when more time since surgery has elapsed, is in accordance with the normal early postoperative rise and fall of CRP, caused by inflammation by the surgery itself. In addition, patients who are still in the hospital more than one week after their surgery, are more likely to have complications. Consequently, CRP measurements beyond this first week are possibly more based on clinical suspicion compared to the more routinely performed measurements in the first postoperative week. On the other hand, non-infectious postoperative complications such as fluid overload, non-septic shock, thrombosis and hypoxemia can lead to inflammation and an elevated CRP [16-19]. Altogether, our results show a strong correlation between CRP and infection. In combination with clinical evaluation and additional diagnostic tests, postoperative CRP can aid to diagnose or rule out a postoperative infection.

Besides CRP, other biomarkers like procalcitonin have been studied for their use in the diagnosis of postoperative infections. Procalcitonin levels increase in response to bacterial infection or sepsis, and are considered to be more specific for bacterial infection than CRP[11,20]. However, for the purpose of

diagnosing postoperative infections, procalcitonin has only been studied in small cohorts with conflicting results. In a meta-analysis in cardiac surgery patients, a mean sensitivity of 0.67 (0.47-0.82), and mean specificity of 0.73 (0.65-0.79) were found with a PPV around 50% and a NPV of >90%[21]. This is similar to two other meta-analysis in gastro-intestinal and pancreatic surgery[11,20]. In general, procalcitonin seems to be insufficiently specific for the diagnosis of postoperative infections, although it has a good NPV and could therefore be useful to exclude a postoperative infection when procalcitonin is low. This concurs with our results on CRP. Because we included only observational data and procalcitonin was not routinely measured, no comparison could be made between procalcitonin and CRP. Other biomarkers that have been evaluated as markers for postoperative infections include IL6, IL18, white cell count, neutrophils, lactate and surface receptor CD64[20,22-24]. These studies show that none of these biomarkers was able to diagnose a postoperative infection with a high accuracy.

Between the eight different surgical subspecialties notable differences were observed regarding the association between CRP and postoperative infection. The odd ratios were lowest in the first postoperative week for general surgery, cardiothoracic surgery, and orthopedic surgery (ranging between 1.0 and 5.5). Potentially, larger wound-beds are created in these types of surgical interventions that in turn cause a more extensive postoperative inflammatory reaction. This is in contrast to ENT, maxillofacial surgery and gynecology, which had the highest odd ratios in the first postoperative week (ranging between 2.4 and 19.9).

Fewer postoperative CRP measurements per patient were performed in the RadboudUMC compared to the LUMC. Several factors could account for this difference such as variations in protocols regarding postoperative laboratory ordering, use of change in CRP instead of single CRP values in the diagnosis of infection, or the use of CRP to monitor treatment. Even though the number of CRP measurements differed, the association between CRP and postoperative infections was similar, with a stronger association from the second postoperative week onwards.

This study included a high number of procedures and observational CRP measurements and comprised multiple types of surgery as well as a follow-up time of 30 days. Many previous investigations on the relationship between CRP and postoperative infections included only one surgical subspecialty, fewer procedures and had a shorter follow-up. For example, the meta-analysis of Yeung et al.[12] focused on colorectal surgery, included a total of 6,647 patients from 23 studies, and had a follow-up of seven days postoperatively. In comparison, our study included electronic health care data from 42,125 procedures, providing insight in the clinical use of CRP and the value of CRP as used in clinical practice.

Limitations

Several limitations of this study need to be considered. The use of a large electronic health record database - i.e., 'big data' – made it impossible to verify every infection by manual chart review. Therefore, an action-based definition of infection was used and defined by the start of non-prophylactic antibiotics with a duration of at least 72h and/or an infection-related surgical re-intervention. Importantly, for a random sample of patients (n=100), manual chart review was performed and showed good correspondence between the action-based definition and diagnosis of postoperative infection by experts. It is still possible that patients without a postoperative infection have had antibiotics or a re-intervention and that this was done (partly) based on an elevated CRP. However, the Netherlands has a high standard of antibiotic stewardship and manual labeling has other limitations, e.g., interobserver variability and error rates. A second limitation is that the exact start of an infection could not be determined, but this is always difficult if not impossible. As a practical approach to this dilemma, patients were excluded from the group without a postoperative infection one week before start of infection treatment to avoid CRP measurements in patients with a beginning infection being counted in the group of patients without an infection. Thirdly, for this study we aimed to explore the diagnostic value of CRP to assess a postoperative infection. If we would have had a more prognostic approach differences in duration of surgery, type of anesthesia, and precautious interventions would also have been relevant to prognose a postoperative infection. But for this study,

we did not adjust for these factors, also because not all possible prognostic factors have been measured. Lastly, we excluded patients with a preoperative CRP >2.5 mg/dL to prevent patients with a preoperative infection from being classified as having a postoperative infection. Cole et al.[9] previously showed that about 5% of the patients have a preoperative CRP >3.0 mg/dL which was probably related to comorbidities. Possibly, we have excluded patients with an elevated CRP due to comorbidities instead of preoperative infection. For this study, the inclusion of patients with a preoperative infection would be of greater impact than the exclusion of a patient with an elevated CRP due to comorbidities. In addition, not every patient had a preoperative CRP measured. Therefore, patients with an unknown elevated CRP could have been included in the study. Seemingly, these patients had no reason for measuring a preoperative CRP, making a preoperative infection much less likely. The study of Cole et al. did not show a difference in CRP between patients with- and without an infection in the first postoperative week, irrespective of the preoperative CRP, which agrees with the results of this study.

Summary and Conclusions

This study revealed that the association between CRP levels and postoperative infections is dependent of the CRP level, the time elapsed since surgery and the surgical subspecialty. Currently, CRP assessments are performed within the initial week after surgery, despite their limited clinical significance. Clinicians need to recognize the evolving nature of postoperative CRP values for the diagnosis of postoperative infections and advance to more selective and consciously performed CRP assessments to optimally utilize its diagnostic capacities. Moreover, these results elucidate the difficulty of using CRP in clinical prediction models and are therefore highly significant for the development of new clinical prediction models incorporating CRP.

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Competing interest statement

BG is currently CEO and majority shareholder of Healthplus.ai B.V. and subsidiaries. SvdM works as a data scientist and PhD at Healthplus.ai and LUMC. SvdM owns share options in Healthplus.ai. AvB, HvG, NvG, SA, MdB and the other members of the PERISCOPE study group have no competing interests to declare.

Contributors:

AB: methodology, analysis, writing original draft. SM: methodology, analysis, data-collection, writing-review and editing. BG: data-collection, writing-review and editing, conceptualization. HG: writing-review and editing, conceptualization. NG: methodology, writing-review and editing. SA: writing-review and editing, conceptualization, supervision. MB: writing-review and editing, conceptualization, supervision, guarantor. The periscope study group: data-collection, conceptualization, writing-review and editing.

Data sharing statement: Data are available upon reasonable request.

Figure legends

Figure 1. Absolute numbers of CRP measurements in the first 30 postoperative days for patients with- and without infection.

Figure 2. Distribution of incremental CRP-level strata for patients with- or without a postoperative infection per level of CRP over time.

Legend: Panel A: measurements for patients that had no infection in the first 30 postoperative days.

Panel B: measurements for patients with an infection in the first 30 postoperative days. Only CRP measurements in the 24 hours before or after start of treatment are included. SI conversion factors: to convert CRP to mg/L, multiply values by 10.

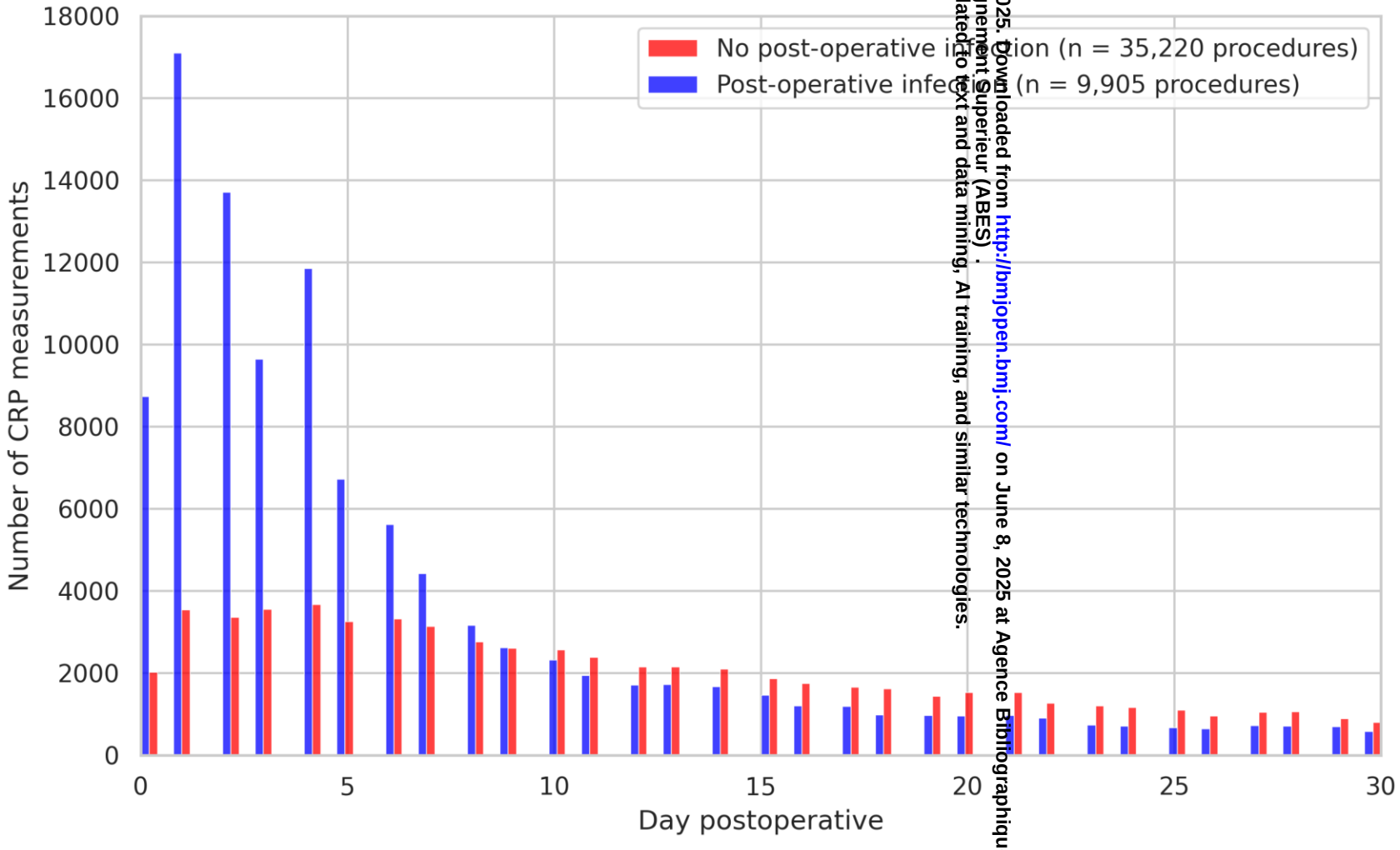
Figure 3. Odds ratios for the association of infection with measured CRP-levels over time in the first 30 postoperative days.

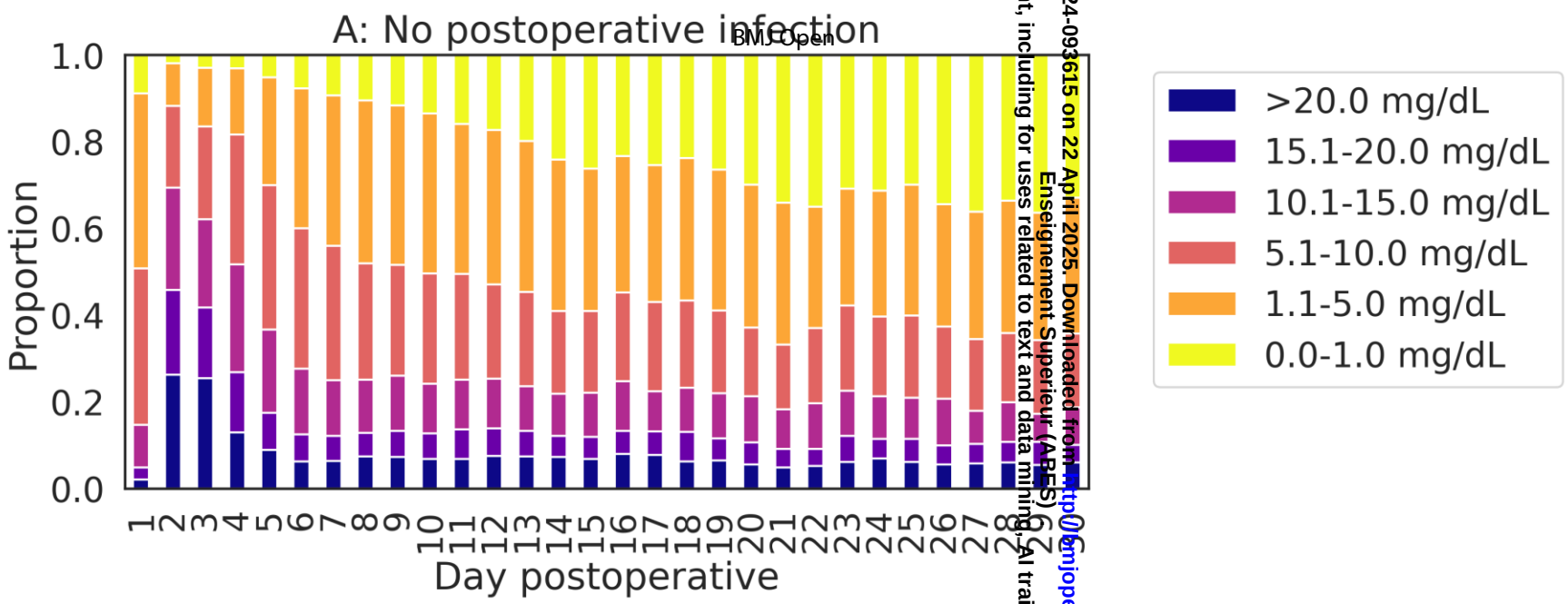
Legend: Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference. Black bars denote 95% confidence intervals. See eTable 3 in the Supplement for the exact values. CRP is reported in mg/dL, to convert to mg/L multiply values by 10.

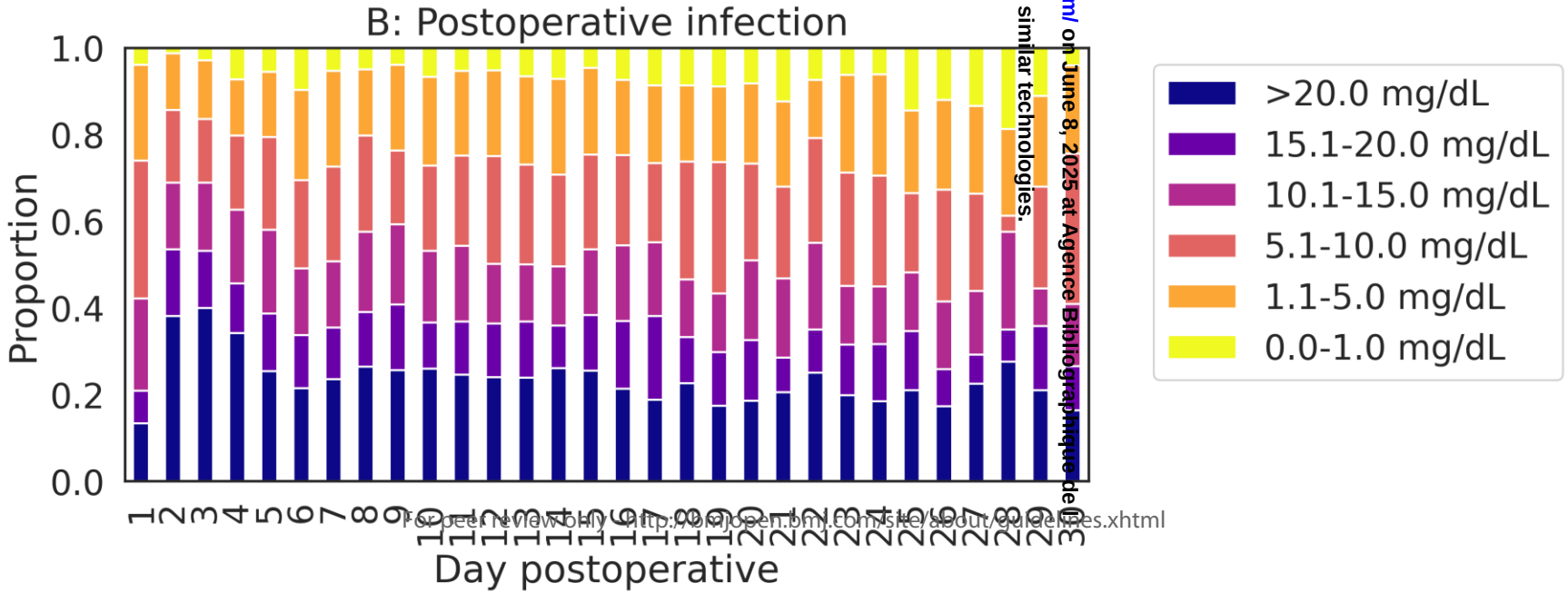
Figure 4. Odds ratios for the association of infection with measured CRP-levels over time in the first 30 postoperative days stratified per surgical subspecialty.

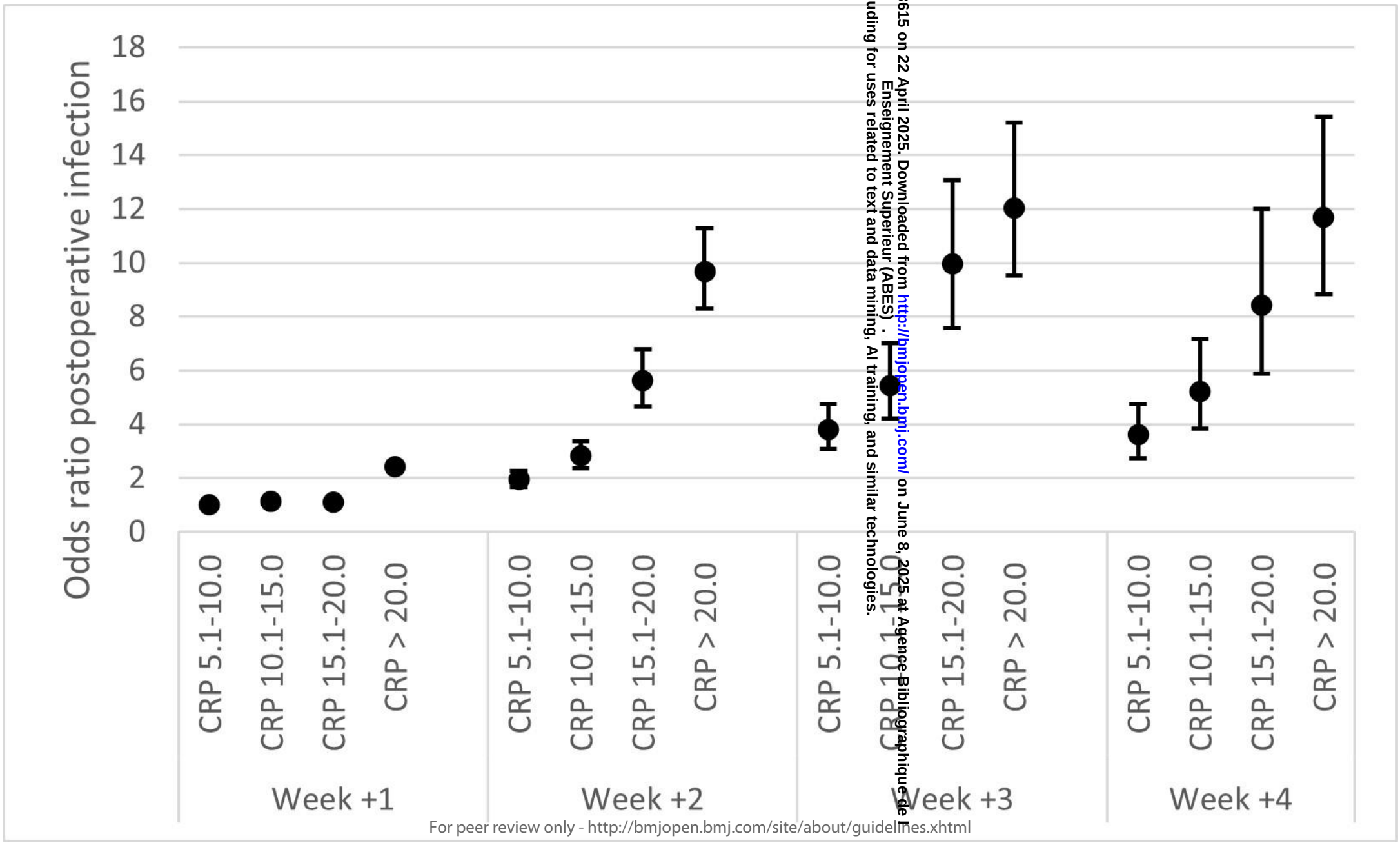
Legend: Abbreviations: Gen: general surgery; Neu: neurosurgery; Uro: urological surgery; Ortho: orthopedic surgery; ENT: ear-nose-throat surgery; Gyn: gynecological surgery; Max: maxillofacial surgery; CTS: cardiothoracic surgery. Week +4 includes days 21-30 postoperative. For calculation of

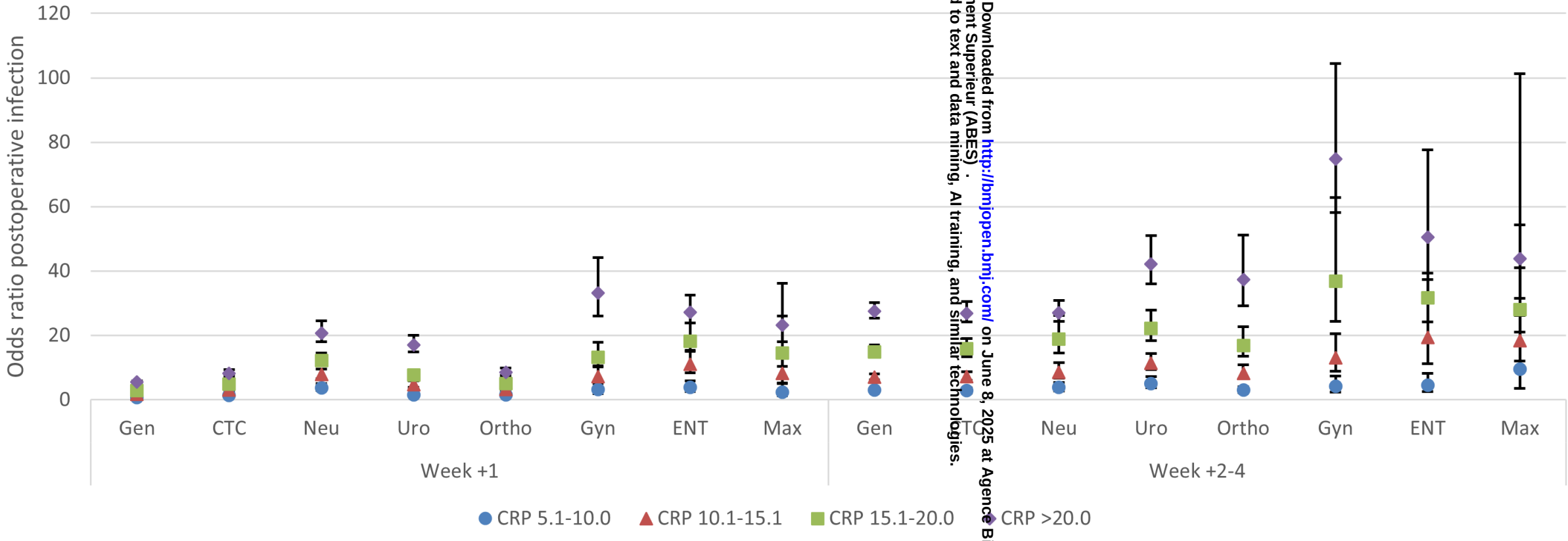
all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference. See eTables 4-11 in the Supplement for exact values. CRP is reported in mg/dL, to convert to mg/L multiply values by 10.







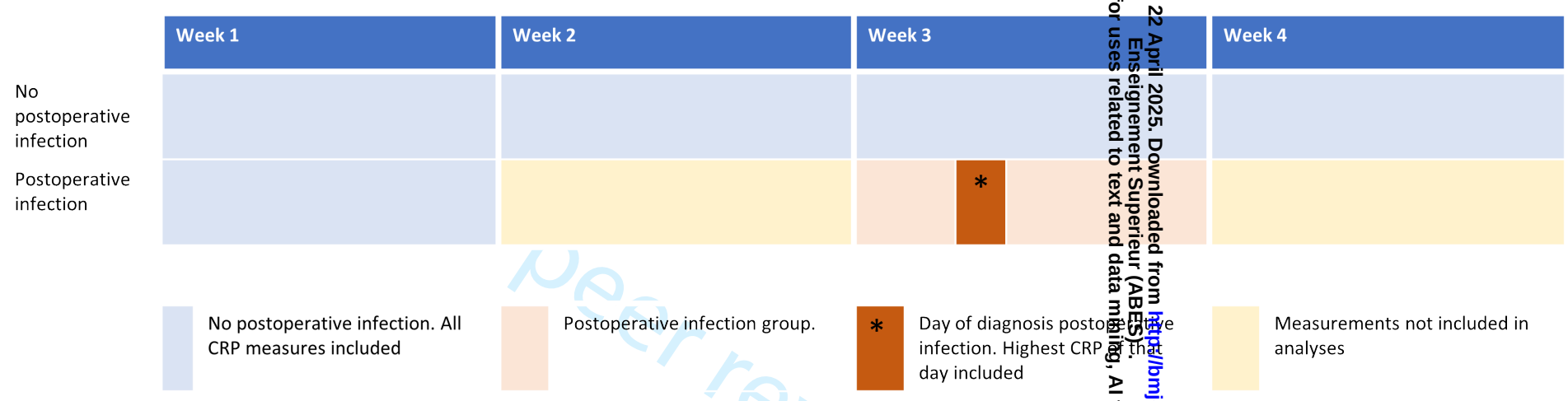




Supplemental Online Content

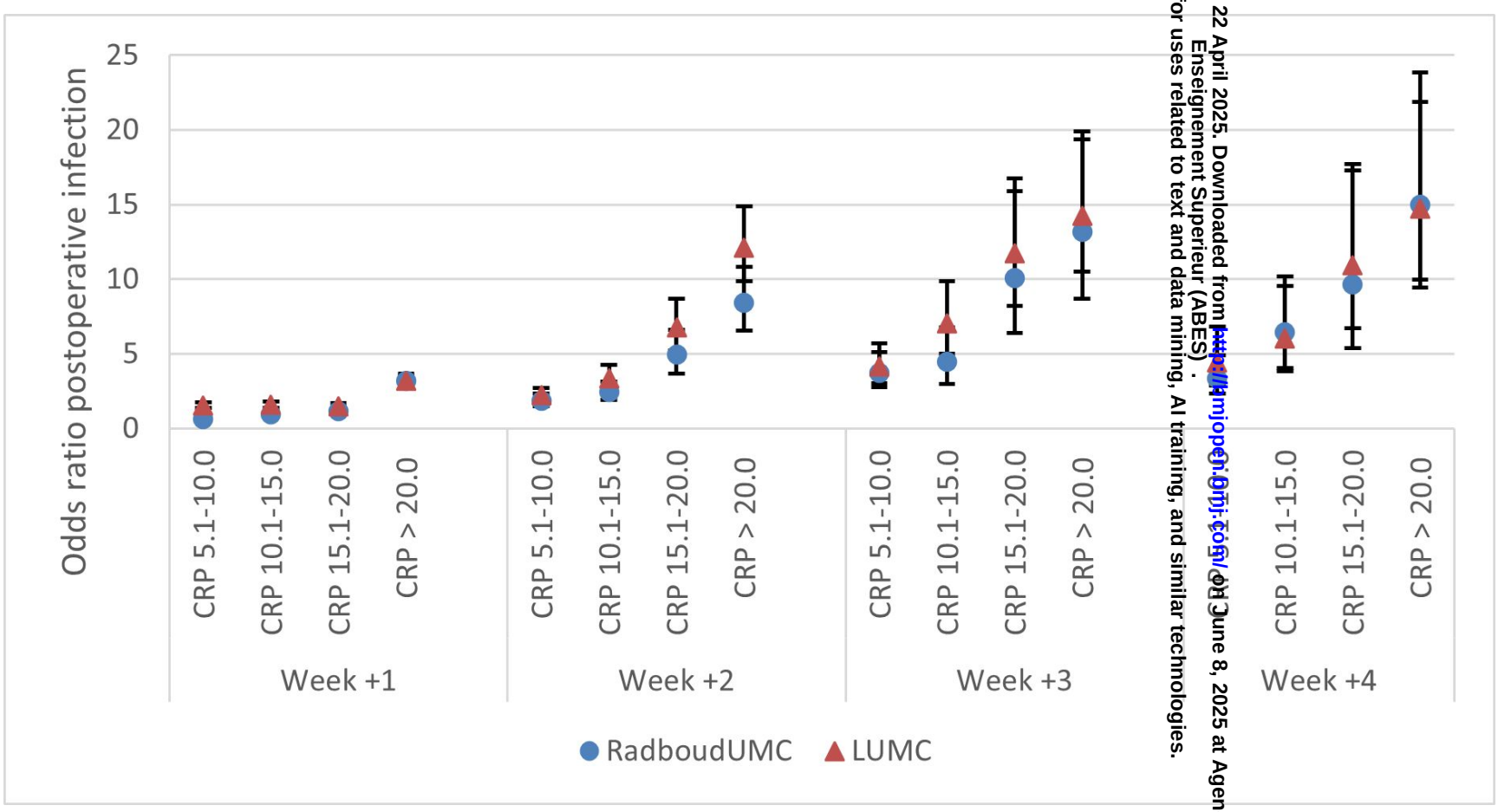
van Boekel AM, van der Meijden SL, Geerts BF, et al. CRP in the first 30 postoperative days and its discriminative value as a marker for postoperative infections.

eFigure 1. Inclusion of CRP measurements of patients with- and without a postoperative infection.



Legend eFigure 1. In this example, a patient developed a postoperative infection in week 3. Therefore, measurements from week 1 were included in the 'No postoperative infection' group, measurements from week 2 and 4 were excluded, and measurements 24 hours before and after the start of therapy in week 3 were included in the 'Postoperative infection' group.

eFigure 2. Odds ratios for the different CRP groups per week postoperative per hospital.



Legend eFigure 2. Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference. Black bars denote 95% confidence intervals. CRP is reported in mg/dL, to convert to mg/L multiply values by 10.

eTable 1. Data extracted from the electronic health record

General surgery and anesthesia information	Local used ID of surgery, description of primary diagnosis, date of surgery, international or national codes for surgery and diagnosis if present (for instance ICD9 or 10), date of diagnosis, date and time of admission, date and time of discharge, admission type (elective/non-elective/day), specialty, location, procedure urgency.
Complications	Complication registration of infectious complications (surgical site infections, pneumonia, urinary tract infection, sepsis, etc.).
Medication	Home medication prescriptions (product name, quantity per day, preferable (local, national or international medication code, like ATC), hospital prescribed medication and administration (Start, Stop date and time, quantity and route of administration).
Laboratory and microbiology results	Chemistry, hematology, blood bank, cultures and stains
Patient data	Age, gender, weight, length, open text on past medical history and procedures (anesthesia pre-assessment field most often) and all anesthesia and surgery questionnaires (incl. operator, time and date).

eTable 2. Infection definition used to identify patients with a postoperative infection within 30 days of surgery

#	Criterion	Condition	Explanation
1	Infection treated with antibiotics	Patient received antibiotic treatment between >= 24 hours and <= 30 days after surgery, with a duration longer than 3 days. BUT NOT extended (beyond 24 hours after surgery) prophylaxis and non-infection related regimens[a]	Infections are treated with antibiotics (ATC codes starting with J01). Some patients (depending on surgery type and patient history) will receive prophylactic antibiotics in the period before, or directly after surgery. To exclude prophylactic antibiotics, treatment has to start after >= 24 h after surgery. Other specific (gastro-intestinal and asplenic) prophylactic regimes are excluded as well. Some patients will receive gastroparesis treatment in the form of erythromycin, which is not to treat a bacterial infection. Sometimes, an infection is suspected for which antibiotics is started, but cultures may come back negative. To exclude these cases, the minimum duration is set at 3 days.
AND/OR			
2	Infection treated with surgical intervention	Patient received a surgical intervention related to treatment of infection within 0 days < surgery < 30 days BUT NOT during initial surgery itself.	(Deep) surgical site infections sometimes require repeated surgery to drain the infection and/or clean the wound. These treatments are done at the operating room and are therefore registered as surgical procedures. The different types of surgical procedures performed at each hospital are filtered on treatments related to postoperative infections.

Abbreviations: ATC code, anatomical therapeutic chemical classification code.

[a]Prophylactic regimes that are excluded are hospital specific. Excluded for this research were:
1. Gastro-intestinal surgery antibiotic prophylaxis; continued on Cefuroxime AND Metronidazole started within 24 hours after surgery up to 5 days. 2. Asplenic patient prophylaxis (1 dd 480 mg Cotrimoxazole (PCP prophylaxis), OR 1 dd 250 mg azithromycin, OR 1 dd 500 mg clarithromycin, OR 1 dd 500mg or 2 dd 250mg amoxicillin (500mg per day in total), OR 1dd 500mg or 2dd 250mg pheneticillin) (500mg per day in total)). 3. Gastroparesis treatment (Low-dose (100 mg) erythromycin)

eTable 3. Comparison of CRP values[a] in patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	1,458	10,346					
Week +2	476	4,404					
Week +3	223	3,058					
Week +4[b]	170	2,760					
CRP 5.1-10.0 mg/dL							
Week +1	817	5,785	1.0 (0.91-1.1)	14.7	64.1	12.4	87.6
Week +2	355	1,690	1.94 (1.67-2.25)	19.4	72.3	17.4	90.2
Week +3	175	630	3.81 (3.07-4.73)	21.1	82.9	21,7	93.2
Week +4[b]	89	401	3.6 (2.73-4.75)	17.5	87.3	18.2	94.2
CRP 10.1-15.0 mg/dL							
Week +1	797	4,992	1.13 (1.03-1.24)	14.4	67.5	13.8	87.6
Week +2	`235	771	2.82 (2.37-3.36)	12.8	85.1	23.4	90.2
Week +3	115	290	5.44 (4.21-7.02)	13.8	91.3	28.4	93.2
Week +4[b]	69	214	5.23 (3.83-7.15)	13.6	92.8	24.4	94.2
CRP 15.1-20.0 mg/dL							
Week +1	587	3,796	1.1 (0.99-1.22)	10.6	73.2	13.4	87.6
Week +2	232	382	5.62 (4.65-6.79)	12.7	92	37.8	90.2
Week +3	119	164	9.95 (7.58-13.0)	14.3	94.9	42	93.2
Week +4[b]	57	110	8.41 (5.89-12.0)	11.2	96.2	34.1	94.2
CRP >20.0 mg/dL							
Week +1	1,893	5,551	2.42 (2.24-2.61)	34.1	65.1	25.4	87.6

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP >20.0 mg/dL							
Week +2	531	508	9.67 (8.29-11.2)	29	89.7	51.1	90.2
Week +3	199	227	12.02 (9.51-15.1)	23.9	93.1	46.7	93.2
Week +4[b]	123	171	11.68 (8.84-15.4)	24.2	94.2	41.8	94.2

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 4. Comparison of CRP values[a] in general surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	870	3,459					
Week +2-4[b]	314	3,151					
CRP 5.1-10.0 mg/dL							
Week +1	343	1,912	0.71 (0.62-0.81)	12.1	64.4	15.2	79.9
Week +2-4[b]	215	730	2.96 (2.44-3.58)	17.8	81.2	22.8	90.9
CRP 10.1-15.0 mg/dL							
Week +1	351	1,373	1.02 (0.89-1.17)	12.4	71.6	20.4	79.9
Week +2-4[b]	145	359	4.05 (3.23-5.07)	12	89.8	28.8	90.9
CRP 15.1-20.0 mg/dL							
Week +1	268	946	1.13 (0.97-1.32)	9.5	78.5	22.1	79.9
Week +2-4[b]	158	201	7.89 (6.22-10.02)	13.1	94	44	90.9
CRP >20.0 mg/dL		297					
Week +1	997	1,489	2.66 (2.38-2.97)	35.2	69.9	40.1	79.9
Week +2-4[b]	375		12.67 (10.46-15.34)	31.1	91.4	55.8	90.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 5. Comparison of CRP values[a] in cardiothoracic surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	51	1,623					
Week +2-4[b]	88	2,739					
CRP 5.1-10.0 mg/dL							
Week +1	104	2,440	1.36 (0.97-1.91)	12.8	39.9	4.1	97
Week +2-4[b]	117	1,311	2.78 (2.09-3.69)	22.1	67.6	8.2	96.9
CRP 10.1-15.0 mg/dL							
Week +1	150	2,853	1.67 (1.21-2.31)	18.5	36.3	5	97
Week +2-4[b]	88	629	4.35 (3.2-5.92)	16.6	81.3	12.3	96.9
CRP 15.1-20.0 mg/dL							
Week +1	136	2,383	1.82 (1.31-2.53	16.7	40.5	5.4	97
Week +2-4[b]	86	309	8.66 (6.29-11.92)	16.3	89.9	21.8	96.9
CRP >20.0 mg/dL							
Week +1	371	3,508	3.37 (2.5-4.54)	45.7	31.6	9.6	97
Week +2-4[b]	150	420	11.12 (8.38-14.75)	28.4	86.7	26.3	96.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 6. Comparison of CRP values[a] in neurosurgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	168	2,295					
Week +2-4[b]	144	1,102					
CRP 5.1-10.0 mg/dL							
Week +1	88	321	3.74 (2.82-4.96)	22.7	87.7	21.5	93.2
Week +2-4[b]	70	142	3.77 (2.7-5.27)	20.3	88.6	33	88.4
CRP 10.1-15.0 mg/dL							
Week +1	46	155	4.05 (2.81-5.83)	11.9	93.7	22.9	93.2
Week +2-4[b]	31	50	4.74 (2.93-7.66)	9	95.7	38.3	88.4
CRP 15.1-20.0 mg/dL							
Week +1	30	95	4.31 (2.78-6.69)	7.7	96	24	93.2
Week +2-4[b]	35	26	10.3 (6.02-17.61)	10.1	97.7	57.4	88.4
CRP >20.0 mg/dL							
Week +1	56	89	8.6 (5.95-12.44)	14.4	96.3	38.6	93.2
Week +2-4[b]	65	61	8.15 (5.52-12.04)	18.8	94.8	51.6	88.4

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 7. Comparison of CRP values[a] in urology patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	115	955					
Week +2-4[b]	94	1,062					
CRP 5.1-10.0 mg/dL							
Week +1	68	390	1.45 (1.05-2.0)	12.5	71	14.8	89.3
Week +2-4[b]	78	174	5.06 (3.6-7.11)	19.3	85.9	31	91.9
CRP 10.1-15.0 mg/dL							
Week +1	94	243	3.21 (2.36-4.36)	17.2	79.7	27.9	89.3
Week +2-4[b]	59	105	6.35 (4.33-9.31)	14.6	91	36	91.9
CRP 15.1-20.0 mg/dL							
Week +1	56	156	2.98 (2.08-4.28)	10.3	86	26.4	89.3
Week +2-4[b]	53	56	10.69 (6.95-16.45)	13.1	95	48.6	91.9
CRP >20.0 mg/dL							
Week +1	213	188	9.41 (7.14-12.39)	39	83.6	53.1	89.3
Week +2-4[b]	121	68	20.1 (13.96-28.93)	29.9	94	64	91.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 8. Comparison of CRP values[a] in orthopedic surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	141	645					
Week +2-4[b]	150	1,088					
CRP 5.1-10.0 mg/dL							
Week +1	100	308	1.49 (1.11-1.99)	22.8	67.7	24.5	82.1
Week +2-4[b]	78	192	2.95 (2.16-4.04)	20.6	85	28.9	87.9
CRP 10.1-15.0 mg/dL							
Week +1	60	162	1.69 (1.19-2.39)	13.7	79.9	27	82.1
Week +2-4[b]	52	71	5.31 (3.57-7.89)	13.7	93.9	42.3	87.9
CRP 15.1-20.0 mg/dL							
Week +1	40	101	1.81 (1.2-2.72)	9.1	86.5	28.4	82.1
Week +2-4[b]	37	31	8.66 (5.22-14.38)	9.8	97.2	54.4	87.9
CRP >20.0 mg/dL							
Week +1	97	126	3.52 (2.55-4.85)	22.1	83.7	43.4	82.1
Week +2-4[b]	62	22	20.44 (12.21-34.23)	16.4	98	73.8	87.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 9. Comparison of CRP values[a] in gynecological surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	38	832					
Week +2-4[b]	35	545					
CRP 5.1-10.0 mg/dL							
Week +1	35	246	3.12 (1.93-5.05)	`17.6	77.2	12.5	95.6
Week +2-4[b]	24	90	4.15 (2.36-7.3)	14.5	85.8	21.1	94
CRP 10.1-15.0 mg/dL							
Week +1	24	129	4.07 (2.36-7.01)	12.1	86.6	15.7	95.6
Week +2-4[b]	22	39	8.78 (4.7-16.39)	13.3	93.3	36.1	94
CRP 15.1-20.0 mg/dL							
Week +1	21	77	5.97 (3.34-10.68)	10.6	91.5	21.4	95.6
Week +2-4[b]	23	12	23.88 (11.45-49.79)	12.9	97.3	60.5	94
CRP >20.0 mg/dL							
Week +1	81	89	19.93 (12.8-31.04)	40.7	90.3	47.6	95.6
Week +2-4[b]	61	25	37.99 (21.32-67.68)	37	95.6	70.9	94

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 10. Comparison of CRP values[a] in ear-, nose- and throat surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	61	430					
Week +2-4[b]	35	394					
CRP 5.1-10.0 mg/dL							
Week +1	61	111	3.87 (2.56-5.84)	23.1	79.5	35.5	87.6
Week +2-4[b]	26	64	4.57 (2.58-8.1)	25	86	28.9	91.8
CRP 10.1-15.0 mg/dL							
Week +1	53	52	7.18 (4.5-11.46)	20.1	89.2	50.5	87.6
Week +2-4[b]	17	13	14.72 (6.61-32.78)	16.3	96.8	56.7	91.8
CRP 15.1-20.0 mg/dL							
Week +1	27	27	7.05 (3.88-12.81)	10.2	84.1	50	87.6
Week +2-4[b]	11	10	12.38 (4.92-31.17)	10.6	97.5	52.4	91.8
CRP >20.0 mg/dL							
Week +1	62	48	9.11 (5.74-14.47)	23.5	90	56.4	87.6
Week +2-4[b]	15	9	18.76 (7.66-45.95)	24.4	97.8	62.5	91.8

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10..

eTable 11. Comparison of CRP values[a] in maxillofacial surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	14	107					
Week +2-4[b]	9	141					
CRP 5.1-10.0 mg/dL							
Week +1	18	57	2.41 (1.12-5.2)	23.7	65.2	24	88.4
Week +2-4[b]	11	18	9.57 (3.49-26.23)	32.4	88.7	37.9	94
CRP 10.1-15.0 mg/dL							
Week +1	19	25	5.81 (2.57-13.14)	25	81.1	43.2	88.4
Week +2-4	5	9	8.7 (2.41-31.42)	14.7	94	35.7	94
CRP 15.1-20.0 mg/dL							
Week +1	9	11	6.25 (2.2-17.72)	11.8	90.7	45	88.4
Week +2-4[b]	5	8	9.79 (2.66-36.1)	14.7	94.6	38.5	94
CRP >20.0 mg/dL							
Week +1	16	14	8.73 (3.52-21.65)	21.1	88.4	53.3	88.4
Week +2-4[b]	4	4	15.67 (3.36-73.17)	11.8	97.2	50	94

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 12. Descriptive characteristics of included procedures per hospital

	All procedures (n = 45,125)	LUMC (n = 29,136)	RadboudUMC (n = 15,989)	P-value[a]
Age, y (IQR)	63.0 (52.0-72.0)	63.0 (52.0-72.0)	63.0 (52.0-71.0)	0.019
Male sex, No. (%)	26,120 (57.9)	16,829 (57.8)	9,291 (58.1)	0.479
Procedure urgency[b]				
Elective procedure, No. (%)	33,042 (73.2)	19,810 (68.0)	13,232 (82.8)	<0.001
Non-elective procedure, No. (%)	7,764 (17.2)	5,007 (17.2)	2,757 (17,2)	
Missing, No. (%)	4,319 (9.6)	4,319 (14,8)	0 (0)	
Procedure duration, median (IQR), minutes	176 (95 - 285)	198 (106 - 319)	151 (78 - 222)	<0.001
Type of surgery				
General surgery, No. (%)	14,916 (33.1)	10,929 (37.5)	3,987 (24.9)	<0.001
Cardiothoracic surgery, No. (%)	14,918 (33.1)	10,498 (36.0)	4,420 (27.6)	
Neurosurgery, No. (%)	4,418 (9.8)	3,014 (10.3)	1,404 (8.8)	
Urological surgery, No. (%)	3,758 (8.3)	1,096 (3.8)	2,662 (16.6)	
Orthopedic surgery, No. (%)	3,031 (6.7)	1,338 (4.6)	1,693 (10.6)	
Gynecological surgery, No. (%)	2,200 (4.9)	1,078 (3.7)	1,122 (7.0)	
ENT surgery, No. (%)	1,390 (3.1)	1,018 (3.5)	372 (2.3)	
Maxillofacial surgery, No. (%)	494 (1.1)	165 (0.6)	329 (2.1)	

Abbreviations: ENT, Ear-, nose and throat; IQR, Interquartile range.

[a]The Mann Withney U test for continuous variables and the Chi Square test for categorial variables.

[b]Procedure urgency as registered in the electronic health record registration.

eTable 13. Number of CRP measurements in the LUMC and RadboudUMC

Postoperative week	Patients with CRP measurement	CRP measurements	Measurements per procedure[a]	Average measurements[b]
LUMC				
1	23,914	83,552	3.5	0.28
2	7,983	23,027	2.9	0.09
3	4,934	13,655	2.8	0.06
4	3,919	11,131	2.8	0.05
RadboudUMC				
1	10,954	20,155	1.8	0.14
2	4,856	8,906	1.8	0.06
3	3,364	5,532	1.6	0.04
4	2,919	4,833	1.7	0.04

Abbreviations: CPR, C-reactive protein; LUMC, Leiden University Medical Center.

[a]Average CRP measurements per patient in patients with at least one CRP measurement

[b]Average CRP measurements per procedure (Total procedures LUMC 85,269; total procedures RadboudUMC 77,380)

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

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C-reactive protein in the first 30 postoperative days and its discriminative value as a marker for postoperative infections, a multi-center cohort study

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Abstract

Objective: To assess the association of c-reactive protein (CRP) with postoperative infections for eight different types of surgery using big data.

Design: A multicenter cohort study with longitudinally collected data from electronic health records, collected from January 1, 2011, to September 22, 2023.

Setting: Data of two tertiary medical centers in the Netherlands were used.

Participants: This study included all procedures (42,125 in total) in adult patients undergoing surgery in two tertiary medical centers in the Netherlands.

Outcome measures: The primary outcome was the association between CRP and a postoperative infection in the first 30 days postoperatively. Postoperative infection was defined by an action-based definition, i.e., patients had to be treated for an infection with antimicrobial treatment and/or an intervention (e.g., surgical drainage) to be classified as having a postoperative infection. CRP measurements were divided into a reference group (0-5.0 mg/dL) and four groups for comparison (5.1-10.0 mg/dL, 10.1-15.0 mg/dL, 15.1-20.0 mg/dL and >20.0 mg/dL). Subgroup analyses were performed for eight major surgical subspecialties and for the two medical centers separately.

Results: A total of 175,779 CRP measurements were performed, of which the majority was drawn in the first postoperative week. The odds ratios (ORs) for developing a postoperative infection varied between 1.0 (0.9-1.1 95%CI) and 12.0 (9.5-15.1 95%CI), with a stronger association for the higher level of CRP categories and when more time had elapsed since surgery. Sensitivity ranged between 11% and 34%, specificity ranged between 64 and 95%, the positive- and negative predicting value ranged between 12% and 51%, and 88% and 94% respectively. For the surgical subspecialties and the two hospitals separately, similar results were found.

Conclusion: In this study, an elevated postoperative CRP was associated with postoperative infections with a stronger association for higher CRP levels. The association was stronger if a longer

time had elapsed since surgery, which contrasts with the moment most CRP measurements were done, namely in the first postoperative week. Clinicians should take the evolving value of CRP in mind when using it in the diagnosis of postoperative infections.

Strengths and limitations of this study

- The cohort consisted of a large, 'real world' sample of adults from two different academic hospitals.
- A clinical action-based definition for postoperative infection was used and tested on a random sample of patients with good correspondence.
- To prevent CRP measurements in patients with a beginning infection being counted in the non-infection group, patients were excluded from the non-infection group one week before start of infection treatment, as the exact start of infection could not precisely be determined.

Key words

Postoperative infection, C-reactive protein, Big-data, Diagnostic test

Introduction

More than 300 million surgical procedures are performed worldwide each year[1]. It is estimated that 6.5 to 18 percent of all patients undergoing surgery will develop a postoperative infection in the first 30 postoperative days[2-5]. A large proportion of infections is diagnosed after the eighth postoperative day and increasingly after discharge from the hospital[6,7]. Early diagnosis and treatment are essential to prevent further deterioration of the clinical condition of the patient. Moreover, unnecessary treatment with antibiotics or a reintervention should be avoided. A wide array of serum biomarkers and prediction models have been used to discriminate between patients with- and without a postoperative infection. The most widely available and used marker for this purpose is C-reactive protein (CRP).

C-reactive protein is an acute phase protein, produced in the liver in case of inflammation or infection in response to pro-inflammatory cytokines[8,9]. CRP levels are elevated during the first. postoperative days due to tissue damage caused by the surgery itself, with its peak around the third postoperative day[9,10]. After these first days, CRP slowly declines to its baseline values. Consequently, a high CRP in the first postoperative days often causes a clinical dilemma: it is either an elevated CRP related to the surgical intervention or a first sign of infection.

This knowledge gap still exists as meta-analyses have shown different discriminative accuracies of CRP in patients who underwent surgery, with a C-statistic varying between 0.66 to 1.00[11-13]. These variations in predictive ability may be explained by differences in selected cut-off values, postoperative day of measurement, type of surgery and the type of predicted infection[11-13]. Moreover, most studies have focused on CRP levels solely in the first postoperative week, included only a small number of patients and used different diagnostic criteria for postoperative infection. Therefore, we have analyzed the CRP-data from a large multi-center cohort of postoperative patients, with a follow-up of 30 days and with the use of a standardized definition for postoperative

infection. The aim of this study was to obtain insight into the clinical use of CRP and its potential diagnostic value as a biomarker for the diagnosis of any type of postoperative infection

Methods

Study design and population

We conducted a cohort study with the use of electronic health record databases as part of the PERISCOPE project [14]. The PERSISCOPE study aims to develop, validate and locally retrain a machine learning algorithm for the prediction of postoperative infections with the use of existing data from electronical health records [14].

The databases include detailed information about 158,703 procedures in adult patients (age ≥18 years) that underwent surgery in two large tertiary medical centers in the Netherlands (the Leiden University Medical Center (LUMC) and the Radboud University Medical Center Nijmegen (RadboudUMC)) between 1-1-2011 and 22-9-2023. See eTable 1 in the Supplement for a full list of data types used from the databases. Procedures from eight surgical subspecialties (general surgery, cardiothoracic surgery, neurosurgery, urological surgery, orthopedic surgery, gynecological surgery, ear-nose-throat (ENT) surgery, and maxillofacial surgery) were included. Patients could be included more than once when they underwent multiple surgeries within the study period. Non-invasive procedures (e.g., anesthesiologic or biopsies) were excluded as well as, re-operations within 30 days of the previous surgery.

As there is under-registration of complications in real-life clinical practice[15], a clinical action-based definition of postoperative infection was used in which postoperative infections were defined as the start of non-prophylactic antibiotics (initiated >24 hours postoperatively and with a minimum duration of 72 hours) and/or a surgical intervention for an infection such as drainage and re-operation within 30 days of the index surgery. All types of postoperative infections were included. See eTable 2 in the Supplement for the full definition used for postoperative infection. All CRP values measured up to 30 days postoperatively were included. Patients without any CRP measurement in

the postoperative period or patients with a possible preoperative infection based on the surgical procedure (manually checked with the use of ICD10 codes and other, hospital specific, diagnosis codes) or a preoperative CRP > 2.5 mg/dL in the five days preceding the operative procedure were excluded from all analyses.

Statistical analysis

To analyze the CRP results, patients were divided into two groups based on their infection status for each postoperative week separately. CRP measurements from patients who developed a postoperative infection within 30 days of surgery were included in the group without an infection until one week before developing the postoperative infection, as the precise moment of start of the infection could not be determined retrospectively. In the postoperative infection group only CRP measurements from the 24 hours before and after the start of treatment were included for analyses (eFigure 1 in the Supplement). If multiple CRP values of one patient on the same day were available, the maximum CRP value for that day was used.

Descriptive statistics were used for baseline characteristics. Continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate. Categorical variables were reported as absolute numbers and percentages. The Mann Whitney U test was used for continuous variables as data were not normally distributed. The Chi Square test was used for categorial variables. Odds ratios (ORs) with 95% confidence intervals (95%CI), sensitivity, specificity and negative and positive predictive values were calculated to examine the strength of the association between postoperative infection and CRP (per stratum: 5.1-10.0 mg/dL, 10.1-15.0 mg/dL, 15.1-20.0 mg/dL and >20.0 mg/dL) per postoperative week. The CRP-range of 0-5.0 mg/dL was used as the reference stratum. The stratification of CRP by 5mg/dL was based on consultation of different clinical specialists and clinical expert discussion. A subgroup analysis was performed for the different major surgical subspecialties and for the two hospitals separately. We

judged that most of the time, CRP was measured for a reason, thus, missing CRP data were not missing at random and were therefore not imputed.

All statistical analyses were performed in Python (Python Software Foundation, Beaverton USA, version 3.8).

Ethics

The study was approved by the Medical Ethics Assessment Committee of the LUMC (METC-LDD (Medisch Ethische Toetsingscommissie Leiden-Den Haag-Delft)) and RadboudUMC (METC Oost-Nederland) protocol nr G18.129, the research performed with the data complied to the Dutch legislation, the declaration of Helsinki and good clinical practice. Informed consent was not required as this was a database study with anonymized data.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Results

Of the 158,703 procedures in the database, a total of 45,125 surgical procedures from 40,009 unique patients were included in the study. 113,578 procedures were excluded because they were either a non-invasive procedure (n = 54,461), re-operation within the 30-day postoperative period (n = 12,649), patients did not have a recorded CRP measurement in the 30-day postoperative period (n = 41,125), or because patients had an elevated CRP (>2.5 mg/dL) in the preoperative period (n = 5,343). During the first 30 days postoperatively, 175,779 CRP measurements were recorded, of which the majority (n = 107,002; 61%) was requested in the first week (Figure 1). Lastly, for patients with more than one CRP measurement per day, the maximum value per day was included for the analyses, excluding 4,988 CRP measurements. Therefore, of the 175,779 CRP measurements, 170,791 measurements were included in the final analyses.

In 9,905 (22%) of the procedures a postoperative infection was present. Postoperative infections occurred more often in male patients and in non-elective procedures. All baseline characteristics of the included procedures are summarized in Table 1. CRP levels in patients with- and without a postoperative infection were almost similar in the first days postoperatively. After the first week, patients with a postoperative infection more often had an elevated CRP and a higher CRP compared to patients without a postoperative infection (Figure 2). The OR for developing a postoperative infection increased with higher CRP category and a longer time elapsed since surgery. The ORs varied between 1.0 (CRP 5.1-10.0 mg/dL in the first postoperative week) and 12.0 (CRP >20.0 mg/dL in the third postoperative week) (Figure 3, eTable 3). Sensitivity was low for all weeks and CRP value-categories, ranging between 11% and 34%. Specificity ranged between 64% and 96% and increased with higher CRP categories and a longer time since surgery. The positive predictive value (PPV) of CRP ranged between 12% and 51%. The negative predictive value of a CRP ≤5.0 mg/dL ranged between 88% and 94% (eTable 3).

Table 1. Descriptive characteristics of included surgical procedures.

	All procedures (n = 45,125)	**No postoperative infection (n = 35,220)**	**Postoperative infection (n = 9,905)**	**P-value[a]**
Age, y (IQR)	63.0 (52.0-72.0)	63.0 (52.0-72.0)	63.0 (52.0-71.0)	0.395
Male sex, No. (%)	26,120 (57.9)	20,206 (57.4)	5,914 (59.7)	<0.001
Procedure urgency[b]				
Elective procedure, No. (%)	33,042 (73.2)	25,944 (73.7)	7,098 (71.7)	<0.001
Non-elective procedure, No. (%)	7,764 (17.2)	5,280 (15.0)	2,484 (25.1)	
Missing, No. (%)	4,319 (9.6)	3,946 (11.2)	323 (3.3)	
Procedure duration, median (IQR), minutes	176 (95 - 285)	180 (96 - 291)	163 (94 - 262)	<0.001
Type of surgery				

General surgery, No. (%)	14,916 (33.1)	10,420 (29.6)	4,496 (45.4)	<0.001
Cardiothoracic surgery, No. (%)	14,918 (33.1)	13,416 (38.1)	1,502 (15.2)	
Neurosurgery, No. (%)	4,418 (9.8)	3,577 (10.2)	841 (8.5)	
Urological surgery, No. (%)	3,758 (8.3)	2,650 (7.5)	1,108 (11.2)	
Orthopedic surgery, No. (%)	3,031 (6.7)	2,071 (5.9)	960 (9.7)	
Gynecological surgery, No. (%)	2,200 (4.9)	1,786 (5.1)	414 (4.2)	
ENT surgery, No. (%)	1,390 (3.1)	959 (2.7)	431 (4.4)	
Maxillofacial surgery, No. (%)	494 (1.1)	341 (1.0)	153 (1.5)	

Abbreviations: ENT, Ear-, nose and throat; IQR, Interquartile range.

[a]The Mann Whitney U test for continuous variables and the Chi Square test for categorial variables.

[b]Procedure urgency as registered in the electronic health record registration.

Surgical subspecialties

Eight different surgical subspecialties were included, i.e., general surgery, cardiothoracic surgery, neurosurgery, urological surgery, orthopedic surgery, gynecological surgery, ENT surgery, and maxillofacial surgery. Most CRP measurements were performed after cardiothoracic surgery (90% of the included procedures had at least one CRP measurement in the 30--day postoperative period) and least CRP measurements after maxillofacial surgery (7% of the procedures). In all subspecialties, the association between CRP and postoperative infection was stronger in weeks 2-4 postoperatively as compared to the first week postoperatively (Figure 4). The strength of the association between CRP and postoperative infection differed per surgical subspecialty. Especially in the first postoperative week there was only a small association between CRP and infection in general, cardiothoracic surgery, and orthopedic surgery, see eTables 4-11 in the Supplement for all the subgroup analyses results.

Differences between hospitals

Of the 170,791 CRP measurements included, 131,365 (77%) were performed in the LUMC and 39,426 (23%) in the RadboudUMC, see eTable 12 for the descriptive characteristics of the included procedures per hospital. In the LUMC there were more patients with a CRP measurement as well as more CRP measurements per patient. This difference was largest in the first postoperative week (eTable 13 in the Supplement). The association between CRP and a postoperative infection in the LUMC and RadboudUMC was similar in both hospitals (eFigure 2 in the Supplement).

Discussion

We found that an elevated postoperative CRP was associated with postoperative infections, with a stronger association for a higher level of CRP and longer time elapsed since surgery, while in contrast, most CRP measurements were done in the first postoperative week. Hence, an imbalance seems to exist between the period in which most CRP measurements are performed and when it has the highest diagnostic value.

The stronger association between postoperative CRP and infection when more time since surgery has elapsed, is in accordance with the normal early postoperative rise and fall of CRP, caused by inflammation by the surgery itself. In addition, patients who are still in the hospital more than one week after their surgery, are more likely to have complications. Consequently, CRP measurements beyond this first week are possibly more based on clinical suspicion compared to the more routinely performed measurements in the first postoperative week. On the other hand, non-infectious postoperative complications such as fluid overload, non-septic shock, thrombosis and hypoxemia can lead to inflammation and an elevated CRP [16-19]. Altogether, our results show a strong correlation between CRP and infection. In combination with clinical evaluation and additional diagnostic tests, postoperative CRP can aid to diagnose or rule out a postoperative infection.

Besides CRP, other biomarkers like procalcitonin have been studied for their use in the diagnosis of postoperative infections. Procalcitonin levels increase in response to bacterial infection or sepsis, and are considered to be more specific for bacterial infection than CRP[11,20]. However, for the purpose of

diagnosing postoperative infections, procalcitonin has only been studied in small cohorts with conflicting results. In a meta-analysis in cardiac surgery patients, a mean sensitivity of 0.67 (0.47-0.82), and mean specificity of 0.73 (0.65-0.79) were found with a PPV around 50% and a NPV of >90%[21]. This is similar to two other meta-analysis in gastro-intestinal and pancreatic surgery[11,20]. In general, procalcitonin seems to be insufficiently specific for the diagnosis of postoperative infections, although it has a good NPV and could therefore be useful to exclude a postoperative infection when procalcitonin is low. This concurs with our results on CRP. Because we included only observational data and procalcitonin was not routinely measured, no comparison could be made between procalcitonin and CRP. Other biomarkers that have been evaluated as markers for postoperative infections include IL6, IL18, white cell count, neutrophils, lactate and surface receptor CD64[20,22-24]. These studies show that none of these biomarkers was able to diagnose a postoperative infection with a high accuracy.

Between the eight different surgical subspecialties notable differences were observed regarding the association between CRP and postoperative infection. The odd ratios were lowest in the first postoperative week for general surgery, cardiothoracic surgery, and orthopedic surgery (ranging between 1.0 and 5.5). Potentially, larger wound-beds are created in these types of surgical interventions that in turn cause a more extensive postoperative inflammatory reaction. This contrasts with ENT, maxillofacial surgery, and gynecology, which had the highest odd ratios in the first postoperative week (ranging between 2.4 and 19.9).

Fewer postoperative CRP measurements per patient were performed in the RadboudUMC compared to the LUMC. Several factors could account for this difference such as variations in protocols regarding postoperative laboratory ordering, use of change in CRP instead of single CRP values in the diagnosis of infection, or the use of CRP to monitor treatment. Even though the number of CRP measurements differed, the association between CRP and postoperative infections was similar, with a stronger association from the second postoperative week onwards.

This study included a high number of procedures and observational CRP measurements and comprised multiple types of surgery as well as a follow-up time of 30 days. Many previous investigations on the relationship between CRP and postoperative infections included only one surgical subspecialty, fewer procedures and had a shorter follow-up. For example, the meta-analysis of Yeung et al.[12] focused on colorectal surgery, included a total of 6,647 patients from 23 studies, and had a follow-up of seven days postoperatively. In comparison, our study included electronic health care data from 42,125 procedures, providing insight in the clinical use of CRP and the value of CRP as used in clinical practice.

Limitations

Several limitations of this study need to be considered. The use of a large electronic health record database - i.e., 'big data' – made it impossible to verify every infection by manual chart review. Therefore, an action-based definition of infection was used and defined by the start of non-prophylactic antibiotics with a duration of at least 72h and/or an infection-related surgical re-intervention. Importantly, for a random sample of patients (n=100), manual chart review was performed and showed good correspondence between the action-based definition and diagnosis of postoperative infection by experts. It is still possible that patients without a postoperative infection have had antibiotics or a re-intervention and that this was done (partly) based on an elevated CRP. However, the Netherlands has a high standard of antibiotic stewardship and manual labeling has other limitations, e.g., interobserver variability and error rates. A second limitation is that the exact start of an infection could not be determined, but this is always difficult if not impossible. As a practical approach to this dilemma, patients were excluded from the group without a postoperative infection one week before start of infection treatment to avoid CRP measurements in patients with a beginning infection being counted in the group of patients without an infection. Thirdly, for this study we aimed to explore the diagnostic value of CRP to assess a postoperative infection. If we would have had a more prognostic approach differences in duration of surgery, type of anesthesia, and precautious interventions would also have been relevant to prognose a postoperative infection. But for this study,

we did not adjust for these factors, also because not all possible prognostic factors have been measured. Furthermore, the lack of availability of data on subgroup membership is also the most important reason why we did not perform subgroup analyses to further explore the diagnostic relation between CRP and infection in different subgroups. Lastly, we excluded patients with a preoperative CRP >2.5 mg/dL to prevent patients with a preoperative infection from being classified as having a postoperative infection. Cole et al.[9] previously showed that about 5% of the patients have a preoperative CRP >3.0 mg/dL which was probably related to comorbidities. Possibly, we have excluded patients with an elevated CRP due to comorbidities instead of preoperative infection. For this study, the inclusion of patients with a preoperative infection would be of greater impact than the exclusion of a patient with an elevated CRP due to comorbidities. In addition, not every patient had a preoperative CRP measured. Therefore, patients with an unknown elevated CRP could have been included in the study. Seemingly, these patients had no reason for measuring a preoperative CRP, making a preoperative infection much less likely. The study of Cole et al. did not show a difference in CRP between patients with- and without an infection in the first postoperative week, irrespective of the preoperative CRP, which agrees with the results of this study. Moreover, age, comorbidities and medication use could have influenced the level of CRP as well as the risk of a postoperative infection. Studies on the relation between CRP and community acquired pneumonia and COVID-19 have shown different results for different age- and comorbidity groups [25-27]. Therefore, the strength of the relation between CRP and postoperative infection might differ for patients with certain comorbidities, advancing age or medication use.

Summary and Conclusions

This study revealed that the association between CRP levels and postoperative infections is dependent of the CRP level, the time elapsed since surgery and the surgical subspecialty. Currently, CRP assessments are performed within the initial week after surgery, despite their limited clinical significance. Clinicians need to recognize the evolving nature of postoperative CRP values for the

diagnosis of postoperative infections and advance to more selective and consciously performed CRP assessments to optimally utilize its diagnostic capacities. Moreover, these results elucidate the difficulty of using CRP in clinical prediction models and are therefore highly significant for the development of new clinical prediction models incorporating CRP.

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Competing interest statement

BG is currently CEO and majority shareholder of Healthplus.ai B.V. and subsidiaries. SvdM works as a data scientist and PhD at Healthplus.ai and LUMC. SvdM owns share options in Healthplus.ai. AvB, HvG, NvG, SA, MdB and the other members of the PERISCOPE study group have no competing interests to declare.

Contributors:

AB: methodology, analysis, writing original draft. SM: methodology, analysis, data-collection, writing-review and editing. BG: data-collection, writing-review and editing, conceptualization. HG: writing-review and editing, conceptualization. NG: methodology, writing-review and editing. SA: writing-review and editing, conceptualization, supervision. MB: writing-review and editing, conceptualization, supervision, guarantor. The periscope study group: data-collection, conceptualization, writing-review and editing.

Data sharing statement: Data are available upon reasonable request.

Figure legends

Figure 1. Absolute numbers of CRP measurements in the first 30 postoperative days for patients with- and without infection.

Figure 2. Distribution of incremental CRP-level strata for patients with- or without a postoperative infection per level of CRP over time.

Legend: Panel A: measurements for patients that had no infection in the first 30 postoperative days.

Panel B: measurements for patients with an infection in the first 30 postoperative days. Only CRP measurements in the 24 hours before or after start of treatment are included. SI conversion factors: to convert CRP to mg/L, multiply values by 10.

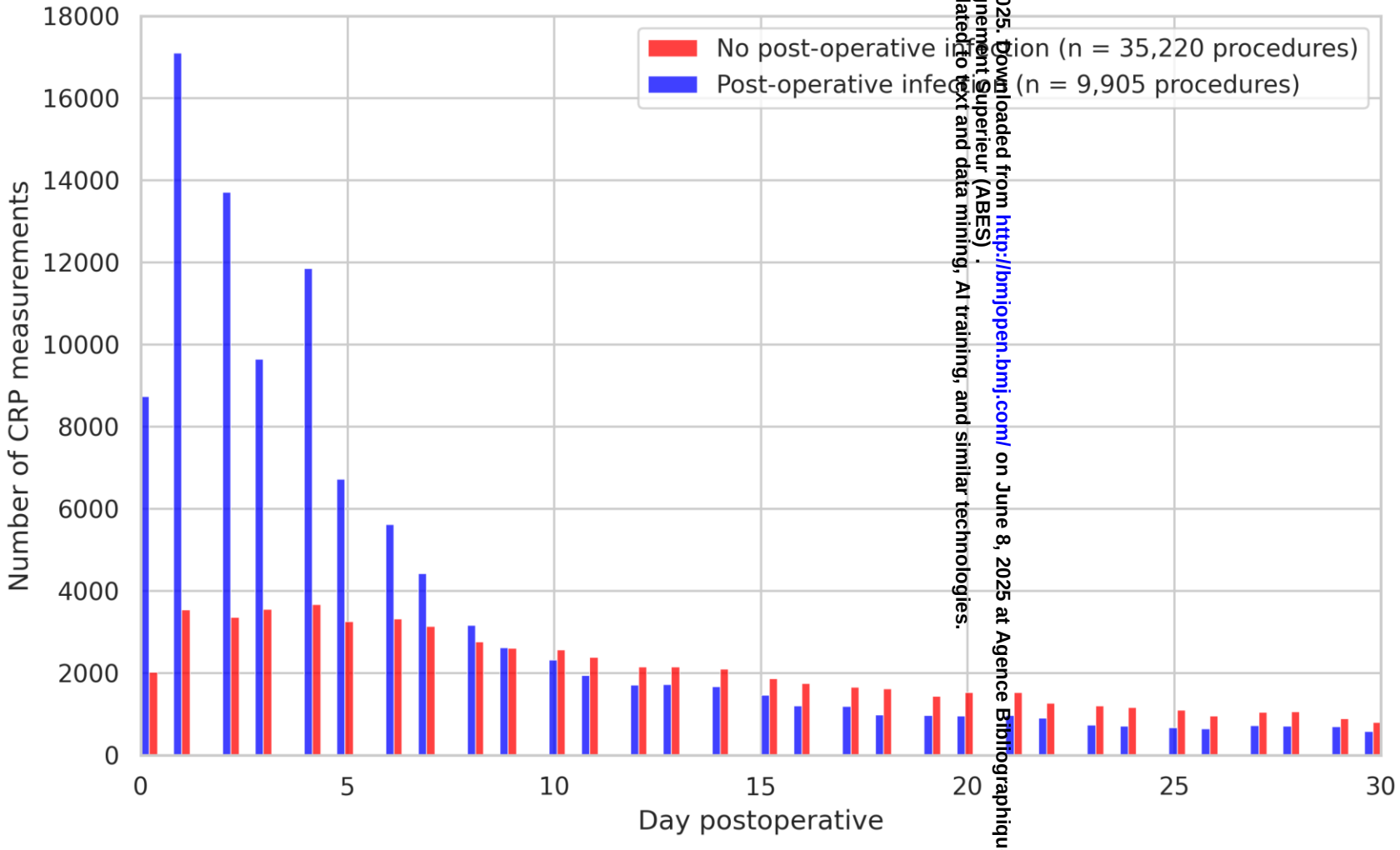
Figure 3. Odds ratios for the association of infection with measured CRP-levels over time in the first 30 postoperative days.

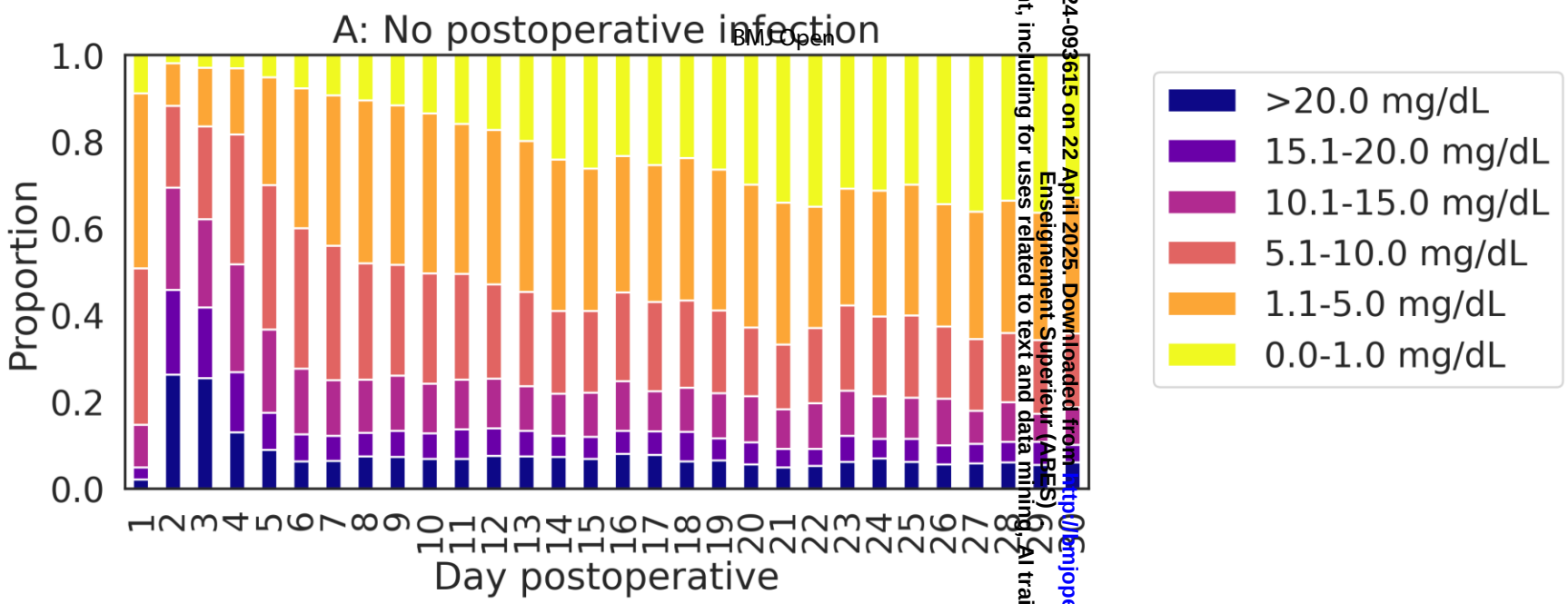
Legend: Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference. Black bars denote 95% confidence intervals. See eTable 3 in the Supplement for the exact values. CRP is reported in mg/dL, to convert to mg/L multiply values by 10.

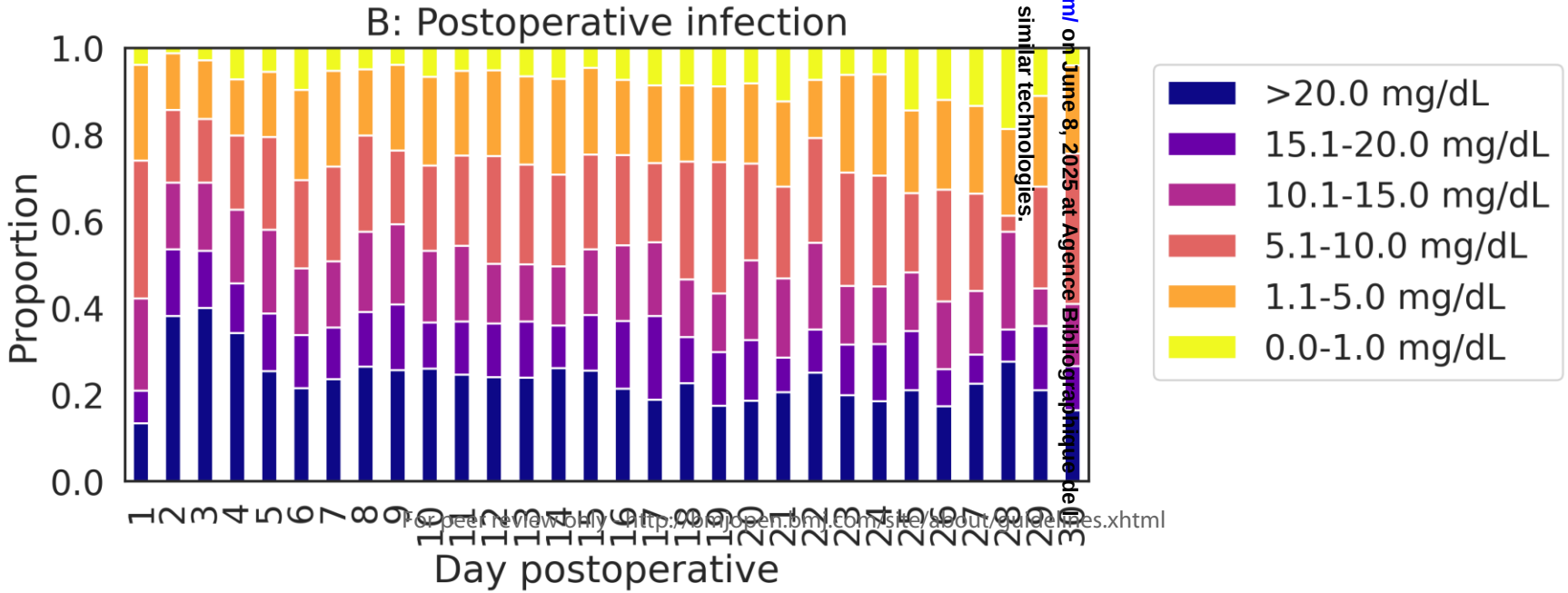
Figure 4. Odds ratios for the association of infection with measured CRP-levels over time in the first 30 postoperative days stratified per surgical subspecialty.

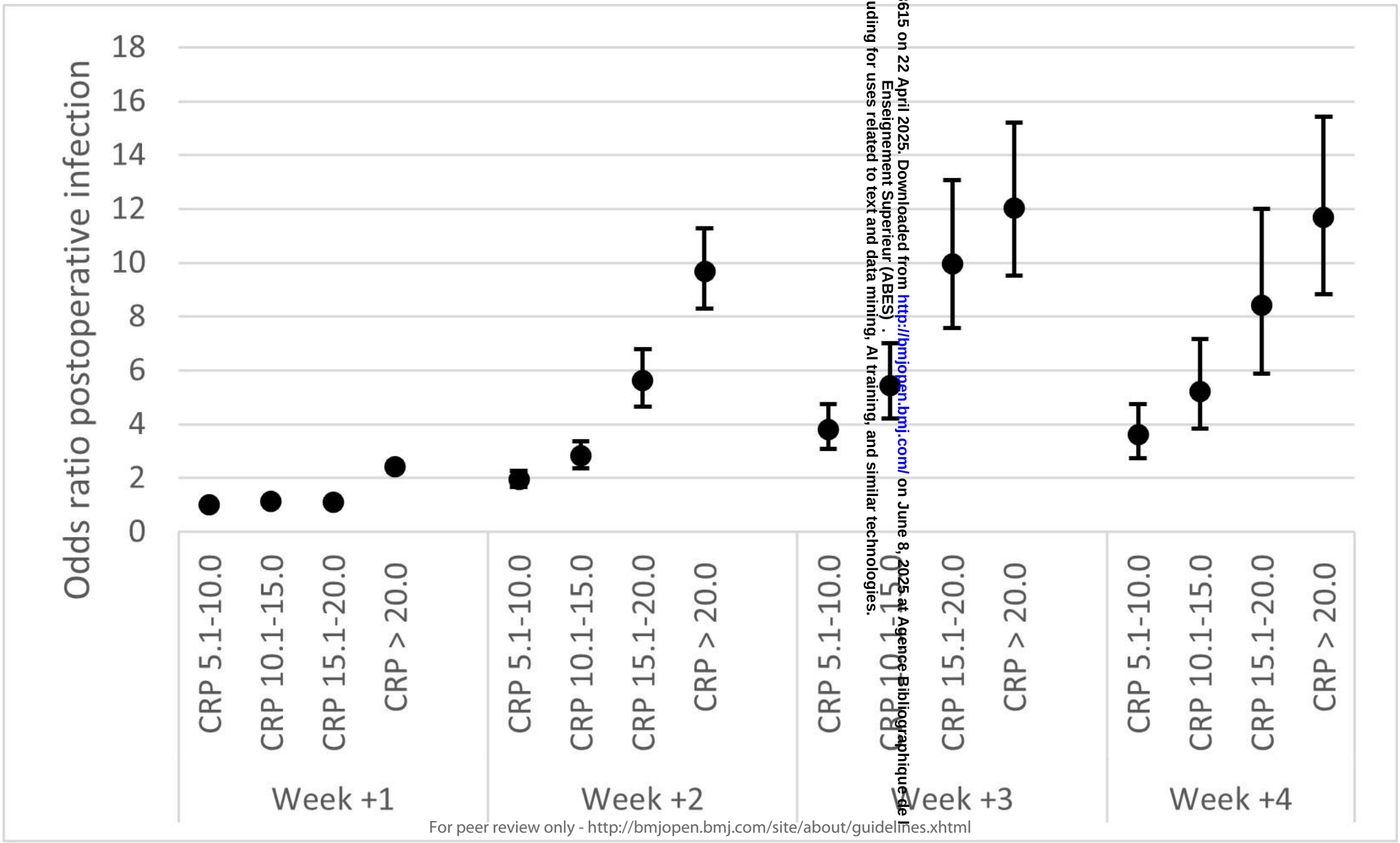
Legend: Abbreviations: Gen: general surgery; Neu: neurosurgery; Uro: urological surgery; Ortho: orthopedic surgery; ENT: ear-nose-throat surgery; Gyn: gynecological surgery; Max: maxillofacial surgery; CTS: cardiothoracic surgery. Week +4 includes days 21-30 postoperative. For calculation of

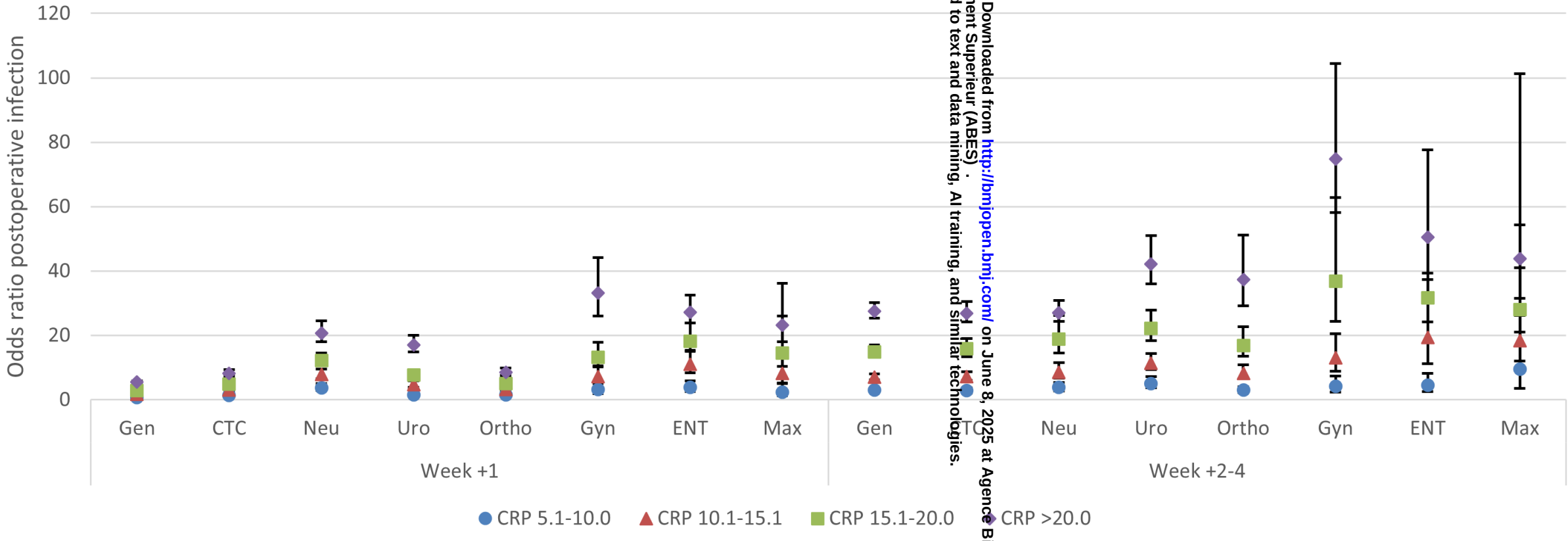
all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference. See eTables 4-11 in the Supplement for exact values. CRP is reported in mg/dL, to convert to mg/L multiply values by 10.







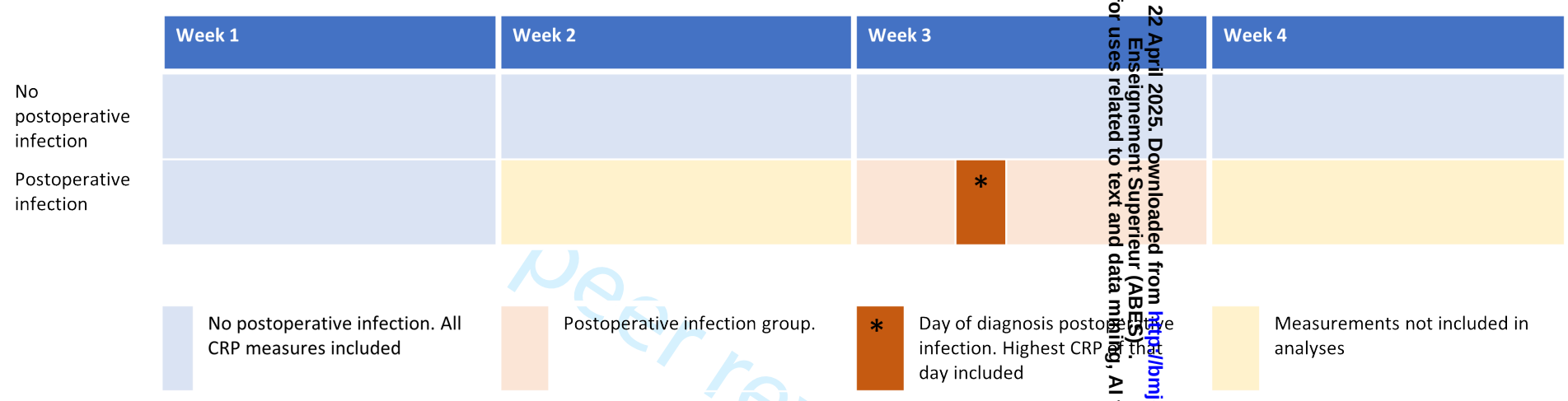




Supplemental Online Content

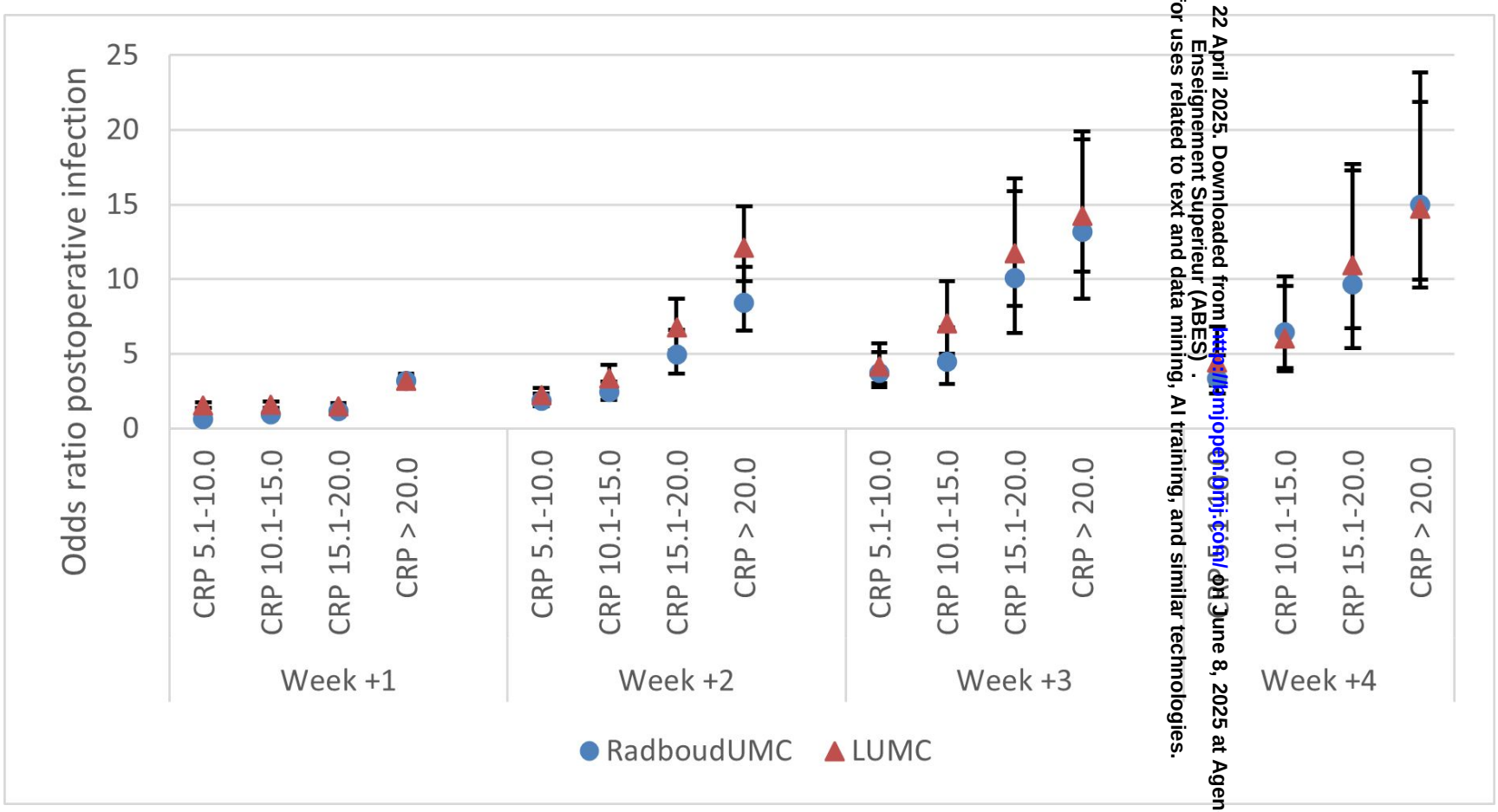
van Boekel AM, van der Meijden SL, Geerts BF, et al. CRP in the first 30 postoperative days and its discriminative value as a marker for postoperative infections.

eFigure 1. Inclusion of CRP measurements of patients with- and without a postoperative infection.



Legend eFigure 1. In this example, a patient developed a postoperative infection in week 3. Therefore, measurements from week 1 were included in the 'No postoperative infection' group, measurements from week 2 and 4 were excluded, and measurements 24 hours before and after the start of therapy in week 3 were included in the 'Postoperative infection' group.

eFigure 2. Odds ratios for the different CRP groups per week postoperative per hospital.



Legend eFigure 2. Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference. Black bars denote 95% confidence intervals. CRP is reported in mg/dL, to convert to mg/L multiply values by 10.

eTable 1. Data extracted from the electronic health record

General surgery and anesthesia information	Local used ID of surgery, description of primary diagnosis, date of surgery, international or national codes for surgery and diagnosis if present (for instance ICD9 or 10), date of diagnosis, date and time of admission, date and time of discharge, admission type (elective/non-elective/day), specialty, location, procedure urgency.
Complications	Complication registration of infectious complications (surgical site infections, pneumonia, urinary tract infection, sepsis, etc.).
Medication	Home medication prescriptions (product name, quantity per day, preferable (local, national or international medication code, like ATC), hospital prescribed medication and administration (Start, Stop date and time, quantity and route of administration).
Laboratory and microbiology results	Chemistry, hematology, blood bank, cultures and stains
Patient data	Age, gender, weight, length, open text on past medical history and procedures (anesthesia pre-assessment field most often) and all anesthesia and surgery questionnaires (incl. operator, time and date).

eTable 2. Infection definition used to identify patients with a postoperative infection within 30 days of surgery

#	Criterion	Condition	Explanation
1	Infection treated with antibiotics	Patient received antibiotic treatment between >= 24 hours and <= 30 days after surgery, with a duration longer than 3 days. BUT NOT extended (beyond 24 hours after surgery) prophylaxis and non-infection related regimens[a]	Infections are treated with antibiotics (ATC codes starting with J01). Some patients (depending on surgery type and patient history) will receive prophylactic antibiotics in the period before, or directly after surgery. To exclude prophylactic antibiotics, treatment has to start after >= 24 h after surgery. Other specific (gastro-intestinal and asplenic) prophylactic regimes are excluded as well. Some patients will receive gastroparesis treatment in the form of erythromycin, which is not to treat a bacterial infection. Sometimes, an infection is suspected for which antibiotics is started, but cultures may come back negative. To exclude these cases, the minimum duration is set at 3 days.
AND/OR			
2	Infection treated with surgical intervention	Patient received a surgical intervention related to treatment of infection within 0 days < surgery < 30 days BUT NOT during initial surgery itself.	(Deep) surgical site infections sometimes require repeated surgery to drain the infection and/or clean the wound. These treatments are done at the operating room and are therefore registered as surgical procedures. The different types of surgical procedures performed at each hospital are filtered on treatments related to postoperative infections.

Abbreviations: ATC code, anatomical therapeutic chemical classification code.

[a]Prophylactic regimes that are excluded are hospital specific. Excluded for this research were:
1. Gastro-intestinal surgery antibiotic prophylaxis; continued on Cefuroxime AND Metronidazole started within 24 hours after surgery up to 5 days. 2. Asplenic patient prophylaxis (1 dd 480 mg Cotrimoxazole (PCP prophylaxis), OR 1 dd 250 mg azithromycin, OR 1 dd 500 mg clarithromycin, OR 1 dd 500mg or 2 dd 250mg amoxicillin (500mg per day in total), OR 1dd 500mg or 2dd 250mg pheneticillin) (500mg per day in total)). 3. Gastroparesis treatment (Low-dose (100 mg) erythromycin)

eTable 3. Comparison of CRP values[a] in patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	1,458	10,346					
Week +2	476	4,404					
Week +3	223	3,058					
Week +4[b]	170	2,760					
CRP 5.1-10.0 mg/dL							
Week +1	817	5,785	1.0 (0.91-1.1)	14.7	64.1	12.4	87.6
Week +2	355	1,690	1.94 (1.67-2.25)	19.4	72.3	17.4	90.2
Week +3	175	630	3.81 (3.07-4.73)	21.1	82.9	21,7	93.2
Week +4[b]	89	401	3.6 (2.73-4.75)	17.5	87.3	18.2	94.2
CRP 10.1-15.0 mg/dL							
Week +1	797	4,992	1.13 (1.03-1.24)	14.4	67.5	13.8	87.6
Week +2	`235	771	2.82 (2.37-3.36)	12.8	85.1	23.4	90.2
Week +3	115	290	5.44 (4.21-7.02)	13.8	91.3	28.4	93.2
Week +4[b]	69	214	5.23 (3.83-7.15)	13.6	92.8	24.4	94.2
CRP 15.1-20.0 mg/dL							
Week +1	587	3,796	1.1 (0.99-1.22)	10.6	73.2	13.4	87.6
Week +2	232	382	5.62 (4.65-6.79)	12.7	92	37.8	90.2
Week +3	119	164	9.95 (7.58-13.0)	14.3	94.9	42	93.2
Week +4[b]	57	110	8.41 (5.89-12.0)	11.2	96.2	34.1	94.2
CRP >20.0 mg/dL							
Week +1	1,893	5,551	2.42 (2.24-2.61)	34.1	65.1	25.4	87.6

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP >20.0 mg/dL							
Week +2	531	508	9.67 (8.29-11.2)	29	89.7	51.1	90.2
Week +3	199	227	12.02 (9.51-15.1)	23.9	93.1	46.7	93.2
Week +4[b]	123	171	11.68 (8.84-15.4)	24.2	94.2	41.8	94.2

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 4. Comparison of CRP values[a] in general surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	870	3,459					
Week +2-4[b]	314	3,151					
CRP 5.1-10.0 mg/dL							
Week +1	343	1,912	0.71 (0.62-0.81)	12.1	64.4	15.2	79.9
Week +2-4[b]	215	730	2.96 (2.44-3.58)	17.8	81.2	22.8	90.9
CRP 10.1-15.0 mg/dL							
Week +1	351	1,373	1.02 (0.89-1.17)	12.4	71.6	20.4	79.9
Week +2-4[b]	145	359	4.05 (3.23-5.07)	12	89.8	28.8	90.9
CRP 15.1-20.0 mg/dL							
Week +1	268	946	1.13 (0.97-1.32)	9.5	78.5	22.1	79.9
Week +2-4[b]	158	201	7.89 (6.22-10.02)	13.1	94	44	90.9
CRP >20.0 mg/dL		297					
Week +1	997	1,489	2.66 (2.38-2.97)	35.2	69.9	40.1	79.9
Week +2-4[b]	375		12.67 (10.46-15.34)	31.1	91.4	55.8	90.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 5. Comparison of CRP values[a] in cardiothoracic surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	51	1,623					
Week +2-4[b]	88	2,739					
CRP 5.1-10.0 mg/dL							
Week +1	104	2,440	1.36 (0.97-1.91)	12.8	39.9	4.1	97
Week +2-4[b]	117	1,311	2.78 (2.09-3.69)	22.1	67.6	8.2	96.9
CRP 10.1-15.0 mg/dL							
Week +1	150	2,853	1.67 (1.21-2.31)	18.5	36.3	5	97
Week +2-4[b]	88	629	4.35 (3.2-5.92)	16.6	81.3	12.3	96.9
CRP 15.1-20.0 mg/dL							
Week +1	136	2,383	1.82 (1.31-2.53	16.7	40.5	5.4	97
Week +2-4[b]	86	309	8.66 (6.29-11.92)	16.3	89.9	21.8	96.9
CRP >20.0 mg/dL							
Week +1	371	3,508	3.37 (2.5-4.54)	45.7	31.6	9.6	97
Week +2-4[b]	150	420	11.12 (8.38-14.75)	28.4	86.7	26.3	96.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 6. Comparison of CRP values[a] in neurosurgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	168	2,295					
Week +2-4[b]	144	1,102					
CRP 5.1-10.0 mg/dL							
Week +1	88	321	3.74 (2.82-4.96)	22.7	87.7	21.5	93.2
Week +2-4[b]	70	142	3.77 (2.7-5.27)	20.3	88.6	33	88.4
CRP 10.1-15.0 mg/dL							
Week +1	46	155	4.05 (2.81-5.83)	11.9	93.7	22.9	93.2
Week +2-4[b]	31	50	4.74 (2.93-7.66)	9	95.7	38.3	88.4
CRP 15.1-20.0 mg/dL							
Week +1	30	95	4.31 (2.78-6.69)	7.7	96	24	93.2
Week +2-4[b]	35	26	10.3 (6.02-17.61)	10.1	97.7	57.4	88.4
CRP >20.0 mg/dL							
Week +1	56	89	8.6 (5.95-12.44)	14.4	96.3	38.6	93.2
Week +2-4[b]	65	61	8.15 (5.52-12.04)	18.8	94.8	51.6	88.4

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 7. Comparison of CRP values[a] in urology patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sen (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	115	955					
Week +2-4[b]	94	1,062					
CRP 5.1-10.0 mg/dL							
Week +1	68	390	1.45 (1.05-2.0)	12.5	71	14.8	89.3
Week +2-4[b]	78	174	5.06 (3.6-7.11)	19.3	85.9	31	91.9
CRP 10.1-15.0 mg/dL							
Week +1	94	243	3.21 (2.36-4.36)	17.2	79.7	27.9	89.3
Week +2-4[b]	59	105	6.35 (4.33-9.31)	14.6	91	36	91.9
CRP 15.1-20.0 mg/dL							
Week +1	56	156	2.98 (2.08-4.28)	10.3	86	26.4	89.3
Week +2-4[b]	53	56	10.69 (6.95-16.45)	13.1	95	48.6	91.9
CRP >20.0 mg/dL							
Week +1	213	188	9.41 (7.14-12.39)	39	83.6	53.1	89.3
Week +2-4[b]	121	68	20.1 (13.96-28.93)	29.9	94	64	91.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 8. Comparison of CRP values[a] in orthopedic surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	141	645					
Week +2-4[b]	150	1,088					
CRP 5.1-10.0 mg/dL							
Week +1	100	308	1.49 (1.11-1.99)	22.8	67.7	24.5	82.1
Week +2-4[b]	78	192	2.95 (2.16-4.04)	20.6	85	28.9	87.9
CRP 10.1-15.0 mg/dL							
Week +1	60	162	1.69 (1.19-2.39)	13.7	79.9	27	82.1
Week +2-4[b]	52	71	5.31 (3.57-7.89)	13.7	93.9	42.3	87.9
CRP 15.1-20.0 mg/dL							
Week +1	40	101	1.81 (1.2-2.72)	9.1	86.5	28.4	82.1
Week +2-4[b]	37	31	8.66 (5.22-14.38)	9.8	97.2	54.4	87.9
CRP >20.0 mg/dL							
Week +1	97	126	3.52 (2.55-4.85)	22.1	83.7	43.4	82.1
Week +2-4[b]	62	22	20.44 (12.21-34.23)	16.4	98	73.8	87.9

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 9. Comparison of CRP values[a] in gynecological surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	38	832					
Week +2-4[b]	35	545					
CRP 5.1-10.0 mg/dL							
Week +1	35	246	3.12 (1.93-5.05)	`17.6	77.2	12.5	95.6
Week +2-4[b]	24	90	4.15 (2.36-7.3)	14.5	85.8	21.1	94
CRP 10.1-15.0 mg/dL							
Week +1	24	129	4.07 (2.36-7.01)	12.1	86.6	15.7	95.6
Week +2-4[b]	22	39	8.78 (4.7-16.39)	13.3	93.3	36.1	94
CRP 15.1-20.0 mg/dL							
Week +1	21	77	5.97 (3.34-10.68)	10.6	91.5	21.4	95.6
Week +2-4[b]	23	12	23.88 (11.45-49.79)	12.9	97.3	60.5	94
CRP >20.0 mg/dL							
Week +1	81	89	19.93 (12.8-31.04)	40.7	90.3	47.6	95.6
Week +2-4[b]	61	25	37.99 (21.32-67.68)	37	95.6	70.9	94

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 10. Comparison of CRP values[a] in ear-, nose- and throat surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	61	430					
Week +2-4[b]	35	394					
CRP 5.1-10.0 mg/dL							
Week +1	61	111	3.87 (2.56-5.84)	23.1	79.5	35.5	87.6
Week +2-4[b]	26	64	4.57 (2.58-8.1)	25	86	28.9	91.8
CRP 10.1-15.0 mg/dL							
Week +1	53	52	7.18 (4.5-11.46)	20.1	89.2	50.5	87.6
Week +2-4[b]	17	13	14.72 (6.61-32.78)	16.3	96.8	56.7	91.8
CRP 15.1-20.0 mg/dL							
Week +1	27	27	7.05 (3.88-12.81)	10.2	84.1	50	87.6
Week +2-4[b]	11	10	12.38 (4.92-31.17)	10.6	97.5	52.4	91.8
CRP >20.0 mg/dL							
Week +1	62	48	9.11 (5.74-14.47)	23.5	90	56.4	87.6
Week +2-4[b]	15	9	18.76 (7.66-45.95)	24.4	97.8	62.5	91.8

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10..

eTable 11. Comparison of CRP values[a] in maxillofacial surgery patients with and without a postoperative infection

	Procedures with POI	Procedures without POI	OR (95% CI)	Sens (%)	Spec (%)	PPV (%)	NPV (%)
CRP 0-5.0 mg/dL							
Week +1	14	107					
Week +2-4[b]	9	141					
CRP 5.1-10.0 mg/dL							
Week +1	18	57	2.41 (1.12-5.2)	23.7	65.2	24	88.4
Week +2-4[b]	11	18	9.57 (3.49-26.23)	32.4	88.7	37.9	94
CRP 10.1-15.0 mg/dL							
Week +1	19	25	5.81 (2.57-13.14)	25	81.1	43.2	88.4
Week +2-4	5	9	8.7 (2.41-31.42)	14.7	94	35.7	94
CRP 15.1-20.0 mg/dL							
Week +1	9	11	6.25 (2.2-17.72)	11.8	90.7	45	88.4
Week +2-4[b]	5	8	9.79 (2.66-36.1)	14.7	94.6	38.5	94
CRP >20.0 mg/dL							
Week +1	16	14	8.73 (3.52-21.65)	21.1	88.4	53.3	88.4
Week +2-4[b]	4	4	15.67 (3.36-73.17)	11.8	97.2	50	94

Abbreviations: CRP, C-reactive protein; POI, postoperative infection; OR, odds ratio; sens, sensitivity; spec, specificity; PPV, positive predicted value; NPV, negative predicted value.

[a]Per included procedure the highest CRP value per week is taken.

[b]Week +4 includes days 21-30 postoperative. For calculation of all odds ratios the CRP-stratum of 0-5.0 mg/dL was taken as a reference.

SI conversion factors: to convert CRP to mg/L, multiply values by 10.

eTable 12. Descriptive characteristics of included procedures per hospital

	All procedures (n = 45,125)	LUMC (n = 29,136)	RadboudUMC (n = 15,989)	P-value[a]
Age, y (IQR)	63.0 (52.0-72.0)	63.0 (52.0-72.0)	63.0 (52.0-71.0)	0.019
Male sex, No. (%)	26,120 (57.9)	16,829 (57.8)	9,291 (58.1)	0.479
Procedure urgency[b]				
Elective procedure, No. (%)	33,042 (73.2)	19,810 (68.0)	13,232 (82.8)	<0.001
Non-elective procedure, No. (%)	7,764 (17.2)	5,007 (17.2)	2,757 (17,2)	
Missing, No. (%)	4,319 (9.6)	4,319 (14,8)	0 (0)	
Procedure duration, median (IQR), minutes	176 (95 - 285)	198 (106 - 319)	151 (78 - 222)	<0.001
Type of surgery				
General surgery, No. (%)	14,916 (33.1)	10,929 (37.5)	3,987 (24.9)	<0.001
Cardiothoracic surgery, No. (%)	14,918 (33.1)	10,498 (36.0)	4,420 (27.6)	
Neurosurgery, No. (%)	4,418 (9.8)	3,014 (10.3)	1,404 (8.8)	
Urological surgery, No. (%)	3,758 (8.3)	1,096 (3.8)	2,662 (16.6)	
Orthopedic surgery, No. (%)	3,031 (6.7)	1,338 (4.6)	1,693 (10.6)	
Gynecological surgery, No. (%)	2,200 (4.9)	1,078 (3.7)	1,122 (7.0)	
ENT surgery, No. (%)	1,390 (3.1)	1,018 (3.5)	372 (2.3)	
Maxillofacial surgery, No. (%)	494 (1.1)	165 (0.6)	329 (2.1)	

Abbreviations: ENT, Ear-, nose and throat; IQR, Interquartile range.

[a]The Mann Withney U test for continuous variables and the Chi Square test for categorial variables.

[b]Procedure urgency as registered in the electronic health record registration.

eTable 13. Number of CRP measurements in the LUMC and RadboudUMC

Postoperative week	Patients with CRP measurement	CRP measurements	Measurements per procedure[a]	Average measurements[b]
LUMC				
1	23,914	83,552	3.5	0.28
2	7,983	23,027	2.9	0.09
3	4,934	13,655	2.8	0.06
4	3,919	11,131	2.8	0.05
RadboudUMC				
1	10,954	20,155	1.8	0.14
2	4,856	8,906	1.8	0.06
3	3,364	5,532	1.6	0.04
4	2,919	4,833	1.7	0.04

Abbreviations: CPR, C-reactive protein; LUMC, Leiden University Medical Center.

[a]Average CRP measurements per patient in patients with at least one CRP measurement

[b]Average CRP measurements per procedure (Total procedures LUMC 85,269; total procedures RadboudUMC 77,380)

SI conversion factors: to convert CRP to mg/L, multiply values by 10.