Pediatric Critical Care Medicine

Identifying children in the intensive care unit at risk of postoperative bacterial infection following cardiothoracic surgery

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Abstract:	Objective: This study examined the predictive value of the biomarkers; Procalcitonin, C-reactive protein, lactate, neutrophils, lymphocytes, platelets and the biphasic APTT waveform to diagnose postoperative bacterial infection. Design: Prospective, observational study. Setting: A regional paediatric intensive care unit and the department of cardiac surgery at Alder Hey Children's NHS Foundation Trust, Liverpool, United Kingdom. Patients: 368 children under the age of 16 were admitted to the PICU were enrolled in the study. Patients not undergoing cardiac surgery were then excluded alongside those with end stage renal or liver disease, moribund or presence of preoperative infection.

	Interventions: Blood samples for the aPTT biphasic waveform and Procalcitonin were collected daily at the same time as part of routine investigations pre and postoperatively until discharge. Children were assessed for postoperative infection until day 28. We excluded children with viral infections and used the Chi-squared test, Mann-Whitney U test, independent sample t test and logistic regression models to determine the predictive value of the biomarkers in those with and without infection. Measurements and Main Results: In total 89/368 (24%) of the children developed bacterial infections (BI) post-operatively, the majority being surgical site infections. In those with BI, Procalcitonin was elevated on post-operative days one, three and the last measurement prior to event (LMPTE). The most significant difference was the LMPTE, 0.67ng/ml in the BI group vs 0.13ng/ml in the non-BI group ($p<0.001$). Longitudinal profiles of PCT and lymphocytes were indistinct in the BI and non-BI groups. Conclusion: None of the biomarkers studied within three days of infection demonstrated a strong predictive value, distinguishing between infection and SIRS in this patient group remains to be difficult.
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Dear Prof. Patrick M. Kochanek (Editor-in-Chief),

We are pleased to submit our manuscript: *Identifying children in the intensive care unit at risk of postoperative bacterial infection following cardiothoracic surgery* by D'Souza et al., for consideration for publication as an original article in *Pediatric Critical Care Medicine*.

This study reports a large prospective cohort study evaluating seven biomarkers of infection (procalcitonin (PCT), C-reactive protein (CRP), lactate, neutrophils, lymphocytes, platelets and the biphasic APTT waveform) in 368 children admitted to intensive care following elective cardiac surgery. In those children who developed bacterial infection following surgery, the most significant difference was seen with PCT in the last measurement prior to developing infection (0.72ng/ml in the bacterial infection group versus 0.13ng/ml in group with no infection, vs 0.46ng/ml in the culture-negative group, vs 0.09ng/ml viral infection group). The longitudinal profiles highlighted that dynamic changes in PCT are more significant than absolute values in distinguishing between the patient groups. An interesting finding from the study was that in those with culture-negative sepsis, PCT increases rapidly in the first two postoperative days before gradually falling until postoperative Day 5, this was distinct to the other patient groups up to postoperative Day 5.

The findings highlighted demonstrate that PCT has faster kinetics than CRP following cardiac surgery and suggest that PCT levels that fail to decrease sufficiently within the first few days postoperatively could indicate an infectious aetiology, this is similar to the findings by Harponiuk et al in 51 children (1) and Jaworski et al in 60 children (2). This could help guide rational antibiotic use by allowing the earlier discontinuation of antibiotics in children where PCT levels fall rapidly after postoperative Day 2. This confers some of the findings by Li et al that dynamic longitudinal monitoring of PCT is more valuable than absolute values and that differentiating infection from cardiopulmonary bypass (CPB)-induced SIRS remains challenging (3). Our study remains unique in the fact that we are the largest study worldwide having enrolled 368 children in four separate patient groups (bacterial infection, viral infection,

culture negative sepsis and no infection) alongside conducting a detailed secondary analysis considering microbiology, site of infection, ventilator-free days 28 (VFD-28) amongst others. Furthermore, we were able to apply the serial data to the prediction of clinically meaningful outcomes, as would occur in routine clinical practice.

We confirm that the manuscript has not been published elsewhere and no other papers based on this work have been submitted. The paper is not under consideration by another journal and should it be published in *Pediatric Critical Care Medicine* it will not be published elsewhere without permission of the editors. All authors have taken a significant role in the conceptualization and completion of the research and have approved the manuscript, agreeing with its submission to *Pediatric Critical Care Medicine*.

Yours Sincerely

Shane D'Souza

Corresponding author

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Identifying children in the intensive care unit at risk of postoperative bacterial infection following cardiothoracic surgery

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Key words: procalcitonin; postoperative infection; cardiac surgery; intensive care; sepsis; congenital heart disease

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Conflict of Interest

The authors declare that they have no conflict of interest.

Contributions

EDC and PB designed the study and provided oversight

RG, RJ, SS, recruited patients and collected data

SD'S collected data and helped draft the manuscript

SD'S drafted the first version of the manuscript

SL performed statistical analysis

SP, KT, PB contributed to study management.

ChC, CD performed laboratory analysis

All authors contributed to drafting the manuscript.

ABSTRACT

Objective: Following surgery, it is difficult to distinguish a post-operative inflammatory reaction from infection. This study examined the predictive value of the biomarkers; procalcitonin (PCT), C-reactive protein (CRP), lactate, neutrophils, lymphocytes, platelets and the biphasic APTT waveform in diagnosing bacterial infection following cardiac surgery.

Design: Prospective, observational study.

Setting: A regional, Paediatric Intensive Care Unit (PICU) in the United Kingdom.

Patients: 368 children under the age of 16 admitted to the PICU for elective cardiac surgery were enrolled in the study.

Interventions: All biomarker measurements were determined daily until post-operative Day 7. Children were assessed for post-operative infection until day 28 and divided into four groups: bacterial infection (BI), culture negative sepsis, viral infection and no infection. We used the Kruskal-Wallis test, Chi-squared test, Analysis of variance (ANOVA), and Area under the curve (AUC) in our analysis.

Measurements and Main Results: In total, 71/368 (19%) children developed BI post-operatively, the majority being surgical site infections. In those with BI, PCT was elevated on post-operative Days 1-3 and the last measurement prior to event (LMPTE) compared to those without BI. The most significant difference was the LMPTE; 0.72ng/ml in the BI group versus 0.13ng/ml in the no infection group (for all groups, $p<0.001$). Longitudinal profiles of all biomarkers were indistinct in the BI and non-BI groups except in those with culture-negative infections who had distinct PCT kinetics on post-operative Days 1-4. Children with culture-negative sepsis required longer ventilatory support and PICU stay and were more likely to develop complications than the other groups.

Conclusion: None of the biomarkers studied within three days of infection distinguished between infection and post-operative inflammatory reaction. However, PCT kinetics peaked on post-operative Day 2 and fell more sharply than CRP kinetics, which

peaked at post-operative Day 3. The monitoring of PCT kinetics following cardiac surgery may help guide rational antimicrobial use.

INTRODUCTION

Sepsis, now defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, presents a significant disease burden, resulting in increased morbidity, mortality, and length of Paediatric Intensive Care Unit (PICU) and hospital stay. Sepsis is a major health concern and it is estimated that 60% of deaths in children under the age of five are attributed to sepsis (1, 2).

The systemic inflammatory response syndrome (SIRS) is a common finding after cardiothoracic surgery, where the problem lies in distinguishing between an invasive bacterial infection – requiring antibiotic therapy - or a general systemic response to the stress of cardiac surgery. SIRS and sepsis often present with closely related clinical signs and significant overlap in presentation, thus, making it difficult to distinguish the two entities even with investigations (Figure 1). Currently, laboratory investigations requested typically include a full blood count (FBC), C-Reactive protein (CRP), alongside bacterial cultures, and viral polymerase chain reaction (PCR) of respiratory secretions (3). However, bacterial cultures - the gold standard for diagnosis, may take 24-48 hours to ascertain the diagnosis.

Accurate and sensitive biomarkers of bacterial infection, providing prognostic information in real time are needed. Clinicians need to prescribe antibiotics to patients displaying SIRS before confirmation of bacterial infection, as delays in initiating treatment for invasive bacterial infection could lead to life-threatening complications. The overuse of antibiotics contributes to the development of antimicrobial resistance, a global health emergency. Antimicrobial resistance is associated with increased hospital costs due to hospital-acquired-infections caused by multidrug resistant organisms and result in in increased morbidity, mortality, and prolonged hospital stay. In the paediatric population,

studies have shown that nosocomial infection cause 20-30% of post-operative complications (4).

Procalcitonin (PCT) is a 116-amino acid precursor of the hormone calcitonin, it is synthesised by the thyroid C cells and pulmonary endocrine cells. In normal health and physiology, it is undetectable in serum. Half-life is approximately 24 hours and independent of renal excretion, research shows that TNFα (as well as IL-1β and IL-6) stimulate PCT release (5). Therefore, PCT is not elevated in viral or fungal infections as it is only released in response to bacteria-specific proinflammatory mediators.

Early in-vitro experimental studies have demonstrated a reduced morbidity and mortality in animals injected with PCT antibodies (6). Studies in children demonstrate that a combined longitudinal measurement of PCT and WCC showing dynamic elevation across post-operative days one through three are significant at differentiating infection from cardiopulmonary bypass (CPB)-induced SIRS (7, 8). However, PCT levels can be increased in other clinical scenarios such as organ rejection, acute respiratory distress syndrome and pancreatitis (9).

Other biomarkers such as the biphasic activated partial thromboplastin time (bAPTT) reflects light transmittance changes in human plasma, which has been shown to be altered in patients with sepsis, presenting a biphasic waveform. This waveform occurs because there is a formation of calcium-dependent complexes between CRP and very low density lipoproteins (VLDL), the resulting consequence is that light transmission decreases before a clot is formed in the first part of the curve (10). As a clinical biomarker, bAPTT in combination with PCT has the potential to be sensitive and specific marker of bacterial sepsis (10).

CRP and platelets are acute phase reactants (APRs) released in response to an inflammatory insult. APRs decrease or increase by 25% during an inflammatory state or tissue injury (11). High CRP levels are not reliable as they represent inflammation for many causes, and not simply infection. A secondary thrombocytosis may occur due to elevated levels of proinflammatory cytokines that are released in response to a tissue insult (12).

Study aims

The aim of this study was to determine the predictive values of seven biomarkers (Procalcitonin (PCT), Biphasic aPTT waveform (bAPTT), C-Reactive Protein (CRP), Lactate, Platelets, Neutrophils and Lymphocytes) to diagnose bacterial infection (BI) post-operatively in children undergoing cardiac surgery.

The secondary aim of the study was to determine the value of the biomarkers in predicting complications such as Time to discharge, Bypass time, Antibiotic duration, PICU-free days (PFD-28), Ventilator-free days (VFD-28), Multiple organ dysfunction syndrome (MODS), Disseminated intravascular coagulation (DIC), and inotrope score at 12 hours.

METHODS

The study was designed as a single-centre prospective case-control study which aimed to determine the utility of biomarkers in the early detection of BI in children admitted to PICU at Alder Hey Children's NHS Foundation Trust in Liverpool (United Kingdom) between October 2010 and June 2012. Alder Hey is a tertiary paediatric centre, covering a paediatric population of over one million children. In total, the study enrolled 657 patients between 0-16 years old; of whom 473 children had undergone surgery, 368 of whom had undergone cardiac surgery. None of them had a BI at admission (Figure 2).

The seven biomarkers (Procalcitonin (PCT), Biphasic aPTT waveform (bAPTT), C-Reactive Protein (CRP), Lactate, Platelets, Neutrophils and Lymphocytes), were measured daily for seven days following PICU admission from blood samples collected at the same time as routine investigations. All assays were carried out using validated or automated methods. PCT was measured using an automated analyser (KRYPTOR-TRACE technology, BRAHMS, Germany). The aPTT biphasic waveform was measured using a MDA-180 analyser (Trinity Biotech UK, Ireland). CRP was measured using an immunoturbidimetric assay on an automated Abbott Architect analyser. Clinicians were blinded to the results of PCT, and bAPTT, which were measured in batches at a later date.

The presence and timing of sepsis was defined according to definitions of the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) with adaptation to children by The International Paediatric Sepsis Conference, 2002 (13). We allocated the patients in to four groups – BI, culture negative sepsis, viral infection and no infection based on the classification of their first infectious episode. Further episodes of infection were excluded from the analysis.

Clinical definitions were based on best practise according to the Centers for Disease Control and Prevention (CDC) (14-17), final adjudication of diagnoses was by a multidisciplinary clinical team who met twice weekly to review PICU cases. The clinical multidisciplinary team consisted of clinicians from PICU, paediatric infectious disease and microbiology.

Definitions

Bacterial infection (BI): children with a definite bacterial infection or a definite bacterial-viral infection as indicated by a positive culture or PCR from a normally sterile site (17). Additionally, we allocated those with presumed bacterial infection to the BI group. This was defined by clinical findings based on a negative surgical site culture but active wound dehiscence or sloughing and purulent drainage from the surgical site.

Culture-negative sepsis: children presenting with signs of sepsis but negative culture or PCR from a sterile site.

Viral infections (VI): children whose infections were confirmed by viral PCR.

No infection: these children had negative cultures and no clinical signs of infection.

Community acquired infection (CAI): was defined as infection that was detected within the first 48 hours of admission (18).

Healthcare associated infections (HAI) were defined as those that occurred > 48 hours after admission (18).

Ventilator associated pneumonia (VAP): where the patient is on mechanical ventilation for >2 calendar days on the date of event, with day of ventilator placement being Day 1, *AND the ventilator was in place on the date of event or the day before (15).

Central line associated bloodstream infection (CLABSI): was defined as a positive blood culture in a patient with a central line (central venous catheter) at the time of (or within 48-hours prior to) the onset of symptoms. Central lines were either a peripherally inserted central catheter (PICC) line, a tunneled catheter or an implanted port (17).

Urinary tract infection (UTI): included symptomatic UTI and catheter-associated UTI, we excluded asymptomatic bacteriuria (17).

Device associated infection (DAI): was defined as the three most common device-associated infections; central line-associated bloodstream infection (CLABSI), ventilator-associated pneumonia (VAP) and catheter-associated urinary tract infection (CAUTI) (17).

Surgical site infection (SSI): Date of event for infection occurs within 30 days after any operative procedure (where Day 1 = the procedure date) and involves only skin and subcutaneous tissue of the incision and patient has at least one of the followings:

a. purulent drainage from the superficial incision.

b. organisms identified from an aseptically-obtained specimen from the superficial incision or subcutaneous tissue by a culture or non-culture based microbiologic testing method which is performed for purposes of clinical diagnosis or treatment.

c. superficial incision that is deliberately opened by a surgeon, attending physician or other designee and culture or non-culture based testing is not performed and patient has at least one of the following signs or symptoms: pain or tenderness; localized swelling; erythema; or heat (14).

Other infection site: was defined as infection that was from multiple or unknown sites, including cultures for gastroenteritis, conjunctivitis, and other respiratory infections.

Multiple organ dysfunction syndrome (MODS): according to the definitions of the ACCP/SCCM Consensus Conference Committee, primary MODS describes an insult in which

organ dysfunction occurs early and can be attributable to it, whereas secondary MODS is the consequence of a host response, in the context of SIRS or sepsis (13).

Disseminated intravascular coagulation (DIC): was defined based on laboratory values indicating low platelets and a raised prothrombin/activated partial thromboplastin time.

We decided to exclude a subsection of patients due to diagnostic uncertainty where there wasn't undisputable evidence of bacterial infection (based on clinical appearance of the wound or where there was no comment) (n=10).

Data was presented as medians and interquartile ranges for all non-normally distributed variables. Receiver operator curves (ROC) were constructed to explore possible thresholds for the diagnosis of infection. Furthermore, we used logistic regression models for predictive analyses, the Chi-squared test for categorical demographic data, the Mann-Whitney U test for continuous data not normally distributed and the Kruskal-Wallis test when making comparisons between the four groups.

RESULTS

Patient demographics

From October 2010 to June 2012, 368 patients who underwent cardiac surgery were recruited to the study, a total of 119 patients went on to develop an infection of which 71 were bacterial infections, viral infections (n=24) and culture-negative sepsis (n=24). In total, 42 different primary ICD10 diagnoses were recorded. The most common isolated defects were septal pathologies which accounted for 27% of patients. Tetralogy of Fallot, patent ductus arteriosus, atrial or ventricular septal defects and Down syndrome-related defects accounted for almost 50% of patients.

In total 20% of the patients were admitted from other hospitals and 28-day mortality was less than 1%. Preoperative baseline characteristics were similar in both those with infection and those without, all children were followed up until day 28 including four who were

followed until death. The demographic differences between children with BI and those in the remaining three groups are highlighted in Table 1. The demographics showed that those with BI were younger in age, median 5 months vs 7 months (no infection) vs 27 months (culture-negative) vs 5 months (viral infection) ($p<0.02$).

Intraoperative progress

Children with culture-negative sepsis spent the longest time in the PICU, 17 PICU-free days (days alive and free from the need for intensive care in the first 28 days) followed by those with BI who spent longer in the PICU (21 PICU-free days) than the other groups; 25 free days (no infection) vs 22.5 (viral) ($p<0.001$). Similarly, those with culture-negative sepsis spent the longest time on ventilatory support, 21 ventilator-free days (days when ventilation was not used in airway management) in the first 28 days post-operation followed by BI with 23 free days vs 26 days (no infection) vs 24 days (viral infection) ($p<0.001$). A total of 88% (n=324) of children underwent cardiopulmonary bypass. The longest cardiopulmonary bypass time was found in those with culture-negative sepsis, 153 minutes vs 132 (BI) vs 101 (no infection) vs 82 (viral infection) ($p=0.003$); cross-clamp time was indistinct across patient groups.

Type of infections and infection sites

In total, 119 suspected infections, were identified (Table 2) including confirmed bacterial and viral infections, bacterial-viral co-infection, presumed bacterial infection and culture-negative sepsis. For the analysis presented here, only confirmed bacterial infections (n=71) including bacterial-viral co-infection are included (BI). BI accounted for 19% of infections in all patients, viral infections (6.5%, n=24), culture negative sepsis (6.5%, n=24) and no infection (65%, n=239) as shown in Table 2. For all infections, the most common site of infection for those with BI was the surgical site (n=43, 61%) followed by unknown/other infection site (n=15, 21%)

and cumulatively, DAI (n=13, 18%). HAI accounted for the majority of infections whilst around 10% were community acquired. Of the 119 infections, 42 led to SIRS (35%) (Table 3).

In total, 59 infections occurred before postoperative Day 8 (BI = 26, culture negative = 16 and VI = 17), whilst 60 infections occurred on or after postoperative Day 8 (BI = 45, culture negative = 8 and VI = 7). We found the AUC curves for infections occurring up to postoperative Day 8 unremarkable with Procalcitonin on Day 1 (0.59 (0.52, 0.65)), Day 2 (0.57 (0.50, 0.65)) and Day 3 (0.59 (0.50, 0.68)).

We found that several of the biomarkers did not accurately differentiate between BI and non-BI groups as illustrated in Table 3. Procalcitonin was increased on the first two days preceding diagnosis of an infection in the BI group. The bAPTT waveform, neutrophils, platelets and lymphocytes showed no significant difference between the BI and non-BI groups of patients.

Furthermore, the graphs depicting longitudinal monitoring do not show differential changes days post-operatively in the BI group for all biomarkers compared to the other patient groups (Fig 3). For patients with BI, PCT values showed a 59% drop between day two and day four postoperatively which was similar to a decrease of 60% in the non-BI group. For CRP, patients with BI had a decrease in CRP by 59% between day two and day four which was again similar to a decrease of 60% in the non-BI group. In those with culture-negative sepsis, PCT and CRP dynamics were distinct on postoperative Days 1-5 compared to the other patient groups. The other biomarkers showed no significant differences between the groups.

Secondary outcome measures

Children with BI were more likely to have MODS which occurred in 20% (n=14) versus 3% in the non-BI group ($p<0.001$). Similarly, DIC was more common in the BI group 24% (n=17) versus 13% in the non-BI group ($p=0.04$). The median length of admission for all patients were 21 PICU-free days 28 (PFD28). CPB, increased cross-clamp time, elevated levels of lactate

and PCT were associated with DIC. CRP, neutrophils, and platelets decreased on all post-operative days in those who developed DIC.

The sub-analysis for MODS showed levels of lactate, PCT, neutrophils, PICU stay duration, CPB, cross-clamp time and duration of ventilation were all significantly increased in children with MODS. Platelet counts were significantly lower in the MODS group across all post-operative days. Other biomarkers showed no statistical significance between patient groups.

DISCUSSION

In this single-centre, prospective cohort study none of the biomarkers studied were significantly elevated in the days preceding infection. In those with BI, the most significant difference was the LMPTE for PCT, 0.72ng/ml in the BI group versus 0.13ng/ml (no infection) vs 0.46ng/ml (culture-negative) vs 0.09ng/ml (viral infection) ($p<0.001$). The longitudinal profiles highlight that dynamic changes in PCT are more significant than absolute values in distinguishing between the patient groups. For all infections occurring prior to postoperative Day 7 and for all infections occurring prior to postoperative Day 28, our AUC values were indiscriminate.

An interesting finding was that in those with culture-negative sepsis, PCT increases rapidly in the first two postoperative days before gradually falling until postoperative Day 5, this was distinct to the other patient groups up to postoperative Day 5. The culture-negative sepsis group is a more homogeneous group than the BI, as this is a group of children with signs of sepsis and ill enough to be admitted to a PICU, which suggests that there is generalised systemic inflammation and possibly organ dysfunction. A total of 38% of those with culture-negative sepsis went on to develop MODS (n=9) versus 20% of those with BI (n=14). By contrast the BI group includes children with SSI, which is a localised infection, and which for most of the cases occurred after postoperative Day 7 when the PCT was not

measured daily, and there was no differential longitudinal profile between BI and non-BI. Although CRP peaked on postoperative Day 3 in the culture-negative sepsis group, it was indistinct for those with BI. The findings highlighted demonstrate that PCT has faster kinetics than CRP following cardiac surgery and suggest that PCT levels that fail to decrease sufficiently within the first few days post-operatively could indicate an infectious aetiology. These findings could help guide rational antibiotic use, by allowing the earlier discontinuation of antibiotics in children where PCT levels fall rapidly after postoperative Day 2. Our findings are in line with those found in other papers where PCT has been monitored longitudinally (8, 19-22). Furthermore, the kinetics of children who were in the culture-negative group mirrored that would be expected of a bacterial infection, suggesting that microbiological diagnostics are failing to confirm a bacterial aetiology, yet clinician acumen suggests using antibiotics in this patient group.

CRP, neutrophils, lymphocytes, bAPTT and platelets showed no significant variation between all patient groups. An explanation for this could be attributed to the major stress placed on the body by surgery and bypass, lymphocyte redistribution is common post-surgery and results in a lymphopenia (23).

When we compared the demographics of the BI and non-BI group, we found that those in the BI group were younger, this can be associated with an immature immune system. Those infected spent longer in the PICU, with a shorter number of PICU free days-28. One potential explanation is that MODS was increased in the BI group compared to the other patient groups. Furthermore, a prolonged period on ventilatory support and a prolonged bypass time were also significantly elevated in the infection group, ventilator associated pneumonia accounted for 14% of infections in the cohort.

In view of this, preventative strategies to reduce post-operative infection, early and accurate diagnosis and prompt treatment would positively impact on utilisation of PICU and hospital resources. Infection prevention and control strategies such as perioperative care

bundles (24), aseptic non-touch technique (25), isolation and the correct use and disposal of personal protective equipment are essential (26) .

PCT and lactate were raised across all postoperative days for patients whom had MODS. Children with DIC had a significantly raised lactate across postoperative Day 1/2 and LMPTE, whereas CRP was decreased across postoperative Day 2/3 in the DIC group. PCT was consistently elevated postoperatively and on the LMPTE in the DIC group. Those with DIC had a prolonged PICU stay, bypass time, cross-clamp time, duration of ventilation and longer duration of antibiotics.

An interesting observation from the study was that children with culture-negative sepsis had the longest cardiopulmonary bypass time, the longest duration of ventilation, the longest duration of antibiotic treatment and the longest PICU stay. As highlighted above, this group of children were likely to be very unwell, with a generalised host response and possible organ dysfunction, so this is not surprising. The longitudinal kinetics for this group showed dynamic increases in PCT, CRP and neutrophils. Clinical judgement of treating this patient group in the same manner as those with BI is justified and adumbrates the need for more sensitive microbiology diagnostics to guide antibiotic prescription and duration.

The strengths of our study were that we investigated a large cohort of patients undergoing a range of cardiothoracic operations. We believe that this is the largest published cohort comparing the most biomarkers, measured longitudinally in children undergoing cardiac surgery. Around 12% of patients did not undergo cardiopulmonary bypass (CPB). This makes our results more generalisable. We measured seven biomarkers longitudinally as well as collected comprehensive data on other outcomes such as DIC and MODS. This makes our study unique in that we were able to apply the serial data to the prediction of clinically meaningful outcomes, as would occur in routine clinical practice.

Our study has some limitations, firstly, a small minority of patients did not receive daily biomarker measurements due to discrepancies with families and clinician led decisions.

Secondly, patients with bacterial and mixed viral-bacterial infections were all grouped together to increase the sample size, some biomarkers are more sensitive to bacterial infections and would not necessarily be elevated in those with co-infections. Finally, as the biomarkers were mostly only measured to postoperative Day 7, a large proportion of patients developed an infection after hospital discharge making the LMPTE difficult to interpret. Without serial measurements after postoperative Day 7, the LMPTE for over 50% of patients (n=60) would have been obtained when the patient was clinically aseptic and recovering from the stressors placed on the body by cardiac surgery. Furthermore, the different types and sources of infection occur at different dates after cardiac surgery, for instance, SSI, which commonly occur between 1-2 weeks postoperatively.

CONCLUSION

Differentiating between an infection and post-operative inflammation continues to remain difficult in this patient group. Longitudinal monitoring was indistinct for those with BI, however, our study showed distinct PCT and CRP kinetics up to postoperative Day 5 in those with culture-negative sepsis. Longitudinal measurements of PCT and CRP and monitoring its dynamic changes provide valuable information and should be considered in the decision-making process to guide rational antibiotic use postoperatively. Children with an infection were more likely to be of a younger age with a prolonged CPB time, increased PICU stay, extended periods of ventilation and susceptible to further complications of MODS and DIC.

FIGURES

Figure 1: Schematic showing the overlap between infection, SIRS and sepsis

Figure 2: CONSORT Diagram and patient flow diagram for study procedures

Figure 3. Serial mean biomarker measurements in children with bacterial infection (solid line)

and without infection (dashed line) during the first seven postoperative days.

LEGENDS

Table 3: Biomarker values in the three days preceding infection (where infection occurs on day three)

[1]Due to the large number of infections occurring post-discharge, we have displayed infections occurring within the first three critical post-operative days as this is when antibiotics are commonly initiated in post-operative prophylaxis (n=34 patients)

Figure 3. Serial mean biomarker measurements in children with bacterial infection (solid line) and without infection (dashed line) during the first seven postoperative days.

TABLES

Table 1: Patient demographics

Table 2: Infection sites and summary

Table 3: Biomarker values up to postoperative day three

SUPPLEMENTAL DIGITAL CONTENTS

Supplementary Table 1: Inclusion and exclusion criteria

Supplementary Table 2: Most frequent primary ICD10 diagnoses

Supplementary Table 3: SIRS breakdown for all patients with an infection

Supplementary Table 4: Last biomarker measurement prior to event

Supplementary Table 5: MODS/DIC status in patient groups

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Figure

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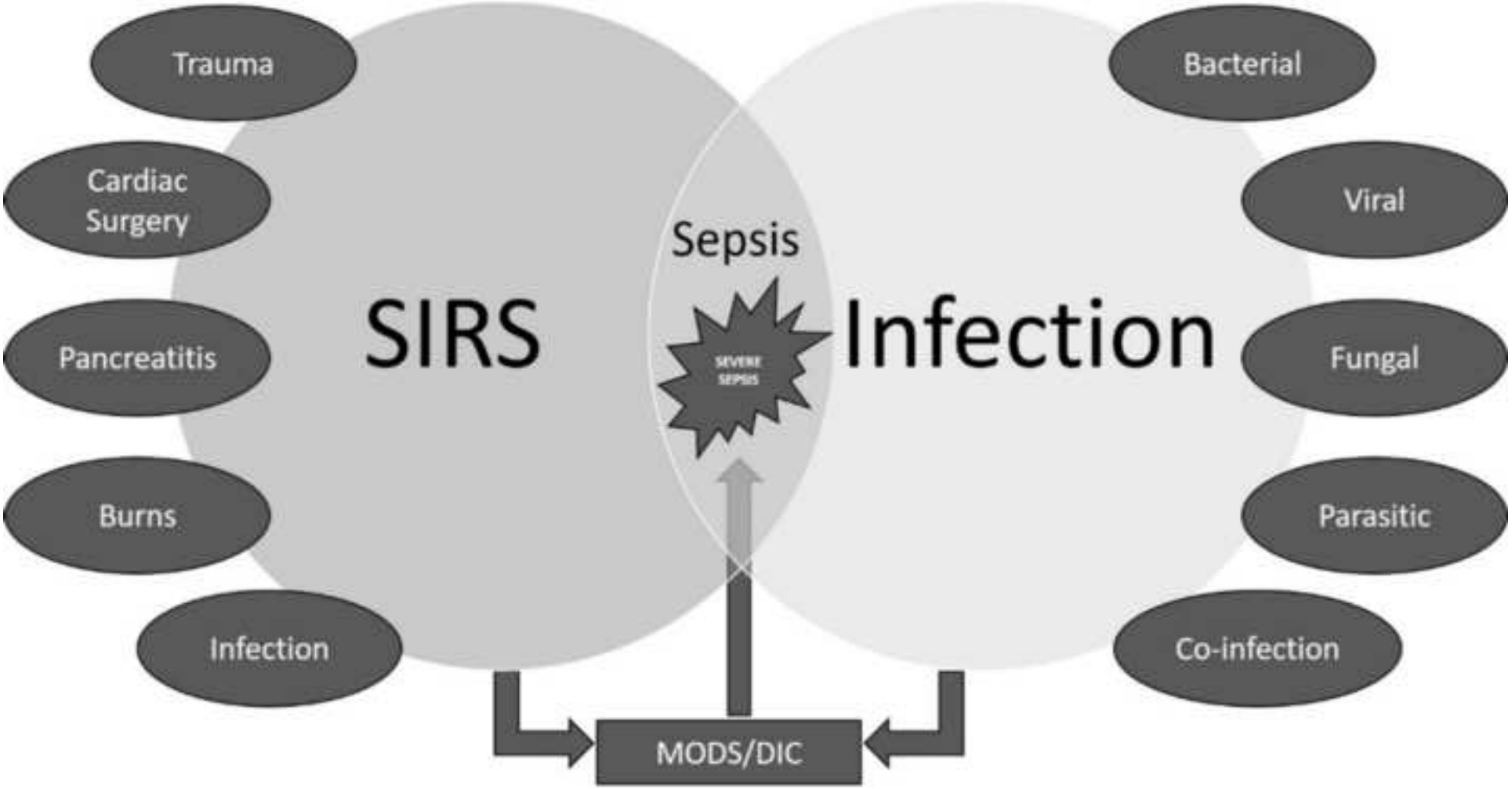
Figure 1



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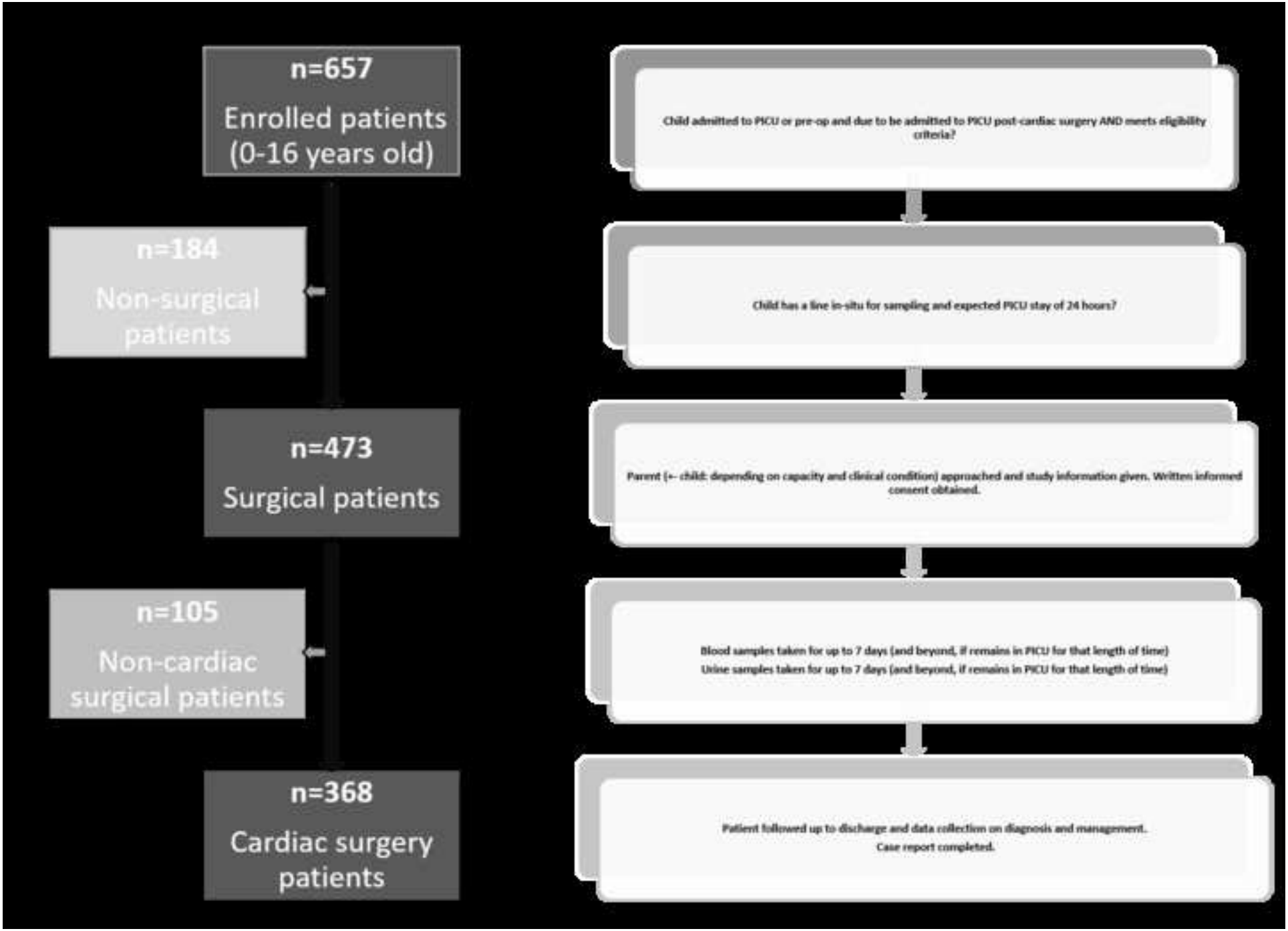

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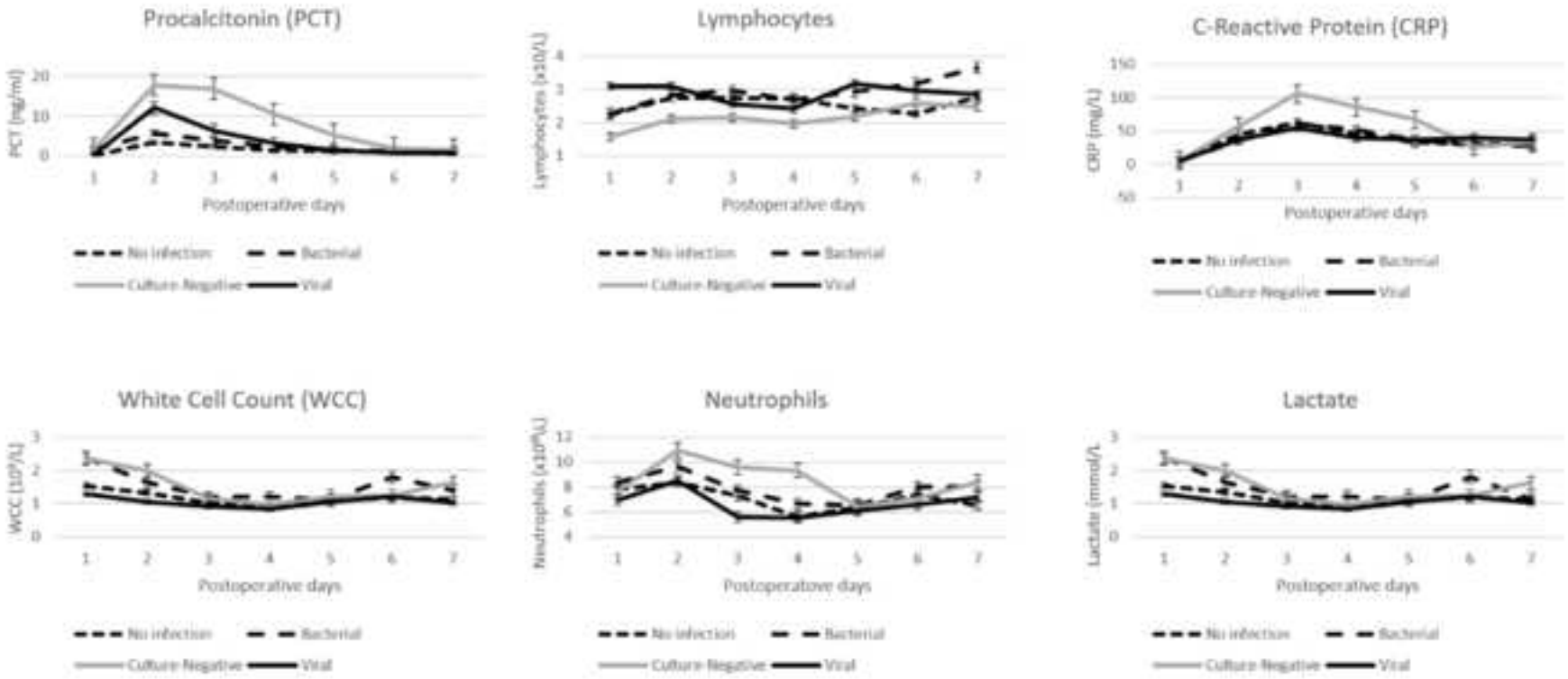

Table 1

Variables	No infection	Bacterial	Culture-negative	Viral	Significance
Gender n(%) Female Male	 119 (49.0) 120 (50.2)	 26 (39.4) 43 (60.6)	 12 (50.0) 12 (50.0)	 9 (33.3) 16 (66.7)	P=0.24[3]
Age (months)[1]	6.84 (34.1) 0.12-194	5.40 (17.0) 0.08-162	27.1 (97.7) 0.12-180	5.28 (8.16) 0.84-92.8	P=0.02[4]
Time to surgery from admission (days)[1]	1 (1) 0-31	1 (3) 0-32	1 (1) 0-9	1 (0) 0-4	NA
Time to discharge from the intensive care unit (days)[1]	3 (4) 1-168	7 (11) 1-63	11 (13) 1-41	5.5 (14) 3-39	NA
Time from surgery to infection (days)[1]		8 (10) 0-28	2 (4) 0-15	1.5 (8) 0-26	NA
Paediatric intensive care unit free days-28 (days)[1]	25 (4) 0-27	21 (11) 0-27	17 (13) 0-27	22.5 (14) 0-25	P<0.001[4]
Bypass (minutes)[1]	101 (82) 0-321	132 (106) 0-273	153 (132) 0-360	82 (98) 0-264	P=0.003[4]
Clamp (minutes)[1]	62 (66) 0-272	75 (86) 0-208	84 (130) 0-231	56.5 (105) 0-211	P=0.62[4]
Multiple organ dysfunction syndrome (n(%)) No Yes	 231 (96.7) 8 (3.3)	 57 (80.3) 14 (19.7)	 15 (62.5) 9 (37.5)	 20 (83.3) 4 (16.7)	NA
Disseminated intravascular coagulation (n(%)) No Yes	 207 (986.6) 32 (13.4)	 54 (76.1) 17 (23.9)	 19 (79.2) 5 (20.8)	 21 (87.5) 3 (17.5)	NA
Mechanical ventilation (days)[1]	0.74 (2) 0-121	3.25 (6) 0-31	5.39 (11) 0-25	2.15 (5) 0-18	NA
Ventilator free days-28 (days)[2]	26.20 (3.21)	23.29 (5.69)	21.38 (7.10)	23.93 (4.56)	P<0.001[5]
Duration of antibiotics (days)[1]	2 (1) 1-18	3 (7) 1-29	7 (7) 2-24	2 (3) 2-18	NA

[1] Median (IQR) and range

[2] Mean (standard deviation)

[3] Chi-squared test

[4] Kruskal-Wallis test

[5] ANOVA

NA – formal statistical test not applicable due to zeros or small counts in some cells.

Table

Table 2

Type of suspected infection	Number of patients (n=368)			
No infection	239			
Confirmed bacterial infection	71			
Culture-negative	24			
Viral infection	24			
Site of infection	**Number of infections, (n=119)**	**Bacterial infection (n=71)**	**Culture negative (n=24)**	**Viral infection (n=24)**
Ventilator associated pneumonia (VAP)	19 (16%)	7 (10%)	9 (37%)	3 (13%)
Central line associated bloodstream infection (CLABSI)	7 (6%)	6 (8%)	1 (4%)	0
Blood stream infection (BSI)	0	0	0	0
Catheter associated Urinary tract infection (CAUTI)	0	0	0	0
Surgical site infection (SSI)	49 (41%)	43 (61%)	3 (13%)	3 (13%)
Other infection site	44 (37%)	15 (21%)	11 (46%)	18 (74%)
Device associated infection (DAI)	26 (22%)	13 (18%)	10 (41%)	3 (13%)

NB: We decided to exclude a subsection of patients due to diagnostic uncertainty where there wasn't undisputable evidence of bacterial infection (based on clinical appearance of the wound or where there was no comment left by clinicians) (n=10)

Table

Table 3

Biomarker and postoperative day of measurement	No infection *(median, (IQR))*	Bacterial infection *(median, (IQR))*	Culture negative *(median, (IQR))*	Viral infection *(median, (IQR))*	Area under the curve *(95% CI)*
Procalcitonin Day 1	0.09 (0.23)	0.16 (0.47)	0.17 (0.54)	0.08 (0.17)	0.59 (0.52, 0.65)
Procalcitonin Day 2	1.40 (2.56)	1.70 (4.34)	4.00 (19.43)	1.62 (2.67)	0.57 (0.50, 0.65)
Procalcitonin Day 3	0.80 (1.38)	1.47 (3.20)	1.60 (16.27)	0.95 (2.08)	0.59 (0.50, 0.68)
bAPTT Day 1	-0.0015 (0.03)	-0.0027 (0.03)	-0.0003 (0.03)	-0.0036 (0.03)	0.49 (0.42, 0.56)
bAPTT Day 2	-0.0142 (0.03)	-0.006 (0.03)	-0.0377 (0.07)	-0.0131 (0.03)	0.51 (0.44, 0.58)
bAPTT Day 3	-0.0136 (0.03)	-0.0226 (0.04)	-0.0567 (0.10)	-0.0168 (0.08)	0.39 (0.31, 0.47)
Neutrophils Day 1	6.68 (4.94)	7.25 (6.35)	7.69 (3.09)	6.50 (5.33)	0.49 (0.42, 0.55)
Neutrophils Day 2	8.16 (4.62)	9.16 (4.94)	11.15 (4.70)	8.01 (3.47)	0.61 (0.53, 0.68)
Neutrophils Day 3	7.07 (3.93)	7.13 (4.05)	9.54 (6.46)	5.06 (3.99)	0.52 (0.43, 0.61)
Platelets Day 1	136 (86)	144 (120)	124 (99)	120 (155)	0.50 (0.43, 0.56)
Platelets Day 2	141 (77)	165 (87)	121.5 (59)	146 (111)	0.51 (0.43, 0.58)
Platelets Day 3	146.5 (101)	140 (74)	120 (64)	149 (1060)	0.43 (0.34, 0.51)
Lymphocytes Day 1	1.81 (1.68)	2.01 (1.87)	1.09 (0.69)	2.47 (2.40)	0.47 (0.40, 0.54)
Lymphocytes Day 2	2.52 (1.86)	2.32 (1.73)	1.69 (1.70)	2.62 (1.75)	0.47 (0.40, 0.55)
Lymphocytes Day 3	2.46 (1.29)	2.44 (1.88)	2.06 (1.54)	2.21 (2.39)	0.46 (0.37, 0.55)
CRP Day 1	4 (0)	4 (0)	4 (0)	4 (0)	0.52 (0.45, 0.59)
CRP Day 2	41.5 (39.5)	32.45 (38.7)	51 (51.1)	31.6 (44.5)	0.44 (0.37, 0.50)
CRP Day 3	49.95 (55)	50.55 (57)	93.05 (74)	39.25 (65)	0.52 (0.44, 0.59)

bAPTT = biphasic activated partial thromboplastin time
CRP = C-Reactive protein

Area under curve – Bacterial/Culture-negative against no infection/Viral (for all infections up to postoperative Day 28)

Biomarker and post-operative day of measurement		**Area under Curve (95%)**
Procalcitonin	Day 1	0.62 (0.55, 0.68)
	Day 2	0.58 (0.50, 0.66)
	Day 3	0.62 (0.52, 0.71)
bAPTT	Day 1	0.49 (0.41, 0.56)
	Day 2	0.52 (0.44, 0.59)
	Day 3	0.40 (0.34, 0.49)
Neutrophils	Day 1	0.50 (0.43, 0.58)
	Day 2	0.63 (0.56, 0.71)
	Day 3	0.58 (0.49, 0.67)
Platelets	Day 1	0.50 (0.42, 0.57)
	Day 2	0.50 (0.43, 0.58)
	Day 3	0.42 (0.34, 0.51)
Lymphocytes	Day 1	0.42 (0.35, 0.50)
	Day 2	0.45 (0.37, 0.52)
	Day 3	0.48 (0.39, 0.57)
CRP	Day 1	0.52 (0.45, 0.59)
	Day 2	0.45 (0.38, 0.52)
	Day 3	0.55 (0.47, 0.63)

Area under curve – Bacterial/Culture-negative against no infection/Viral (for all infections up to postoperative Day 7)

Biomarker and post-operative day of measurement		**Area under Curve (95%)**
Procalcitonin	Day 1	0.59 (0.52, 0.65)
	Day 2	0.57 (0.50, 0.65)
	Day 3	0.59 (0.50, 0.68)
bAPTT	Day 1	0.49 (0.42, 0.56)
	Day 2	0.51(0.44, 0.58)
	Day 3	0.39 (0.31, 0.47)
Neutrophils	Day 1	0.49 (0.42, 0.55)
	Day 2	0.61 (0.53, 0.68)
	Day 3	0.52 (0.43, 0.61)
Platelets	Day 1	0.50 (0.43, 0.56)
	Day 2	0.51 (0.43, 0.58)
	Day 3	0.43 (0.34, 0.51)
Lymphocytes	Day 1	0.47 (0.40, 0.54)
	Day 2	0.47 (0.40, 0.55)
	Day 3	0.46 (0.37, 0.55)
CRP	Day 1	0.52 (0.45, 0.59)
	Day 2	0.44 (0.37, 0.50)
	Day 3	0.52 (0.44, 0.59)