2019-07-12

The Role of Procalcitonin Measurements in Predicting Clinical Outcomes in Critically Ill/Injured Patients

Al Rawahi, Aziza

UNIVERSITY OF CALGARY

The Role of Procalcitonin Measurements in Predicting Clinical Outcomes in Critically Ill/Injured Patients

by

Aziza Al Rawahi

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE

DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN MEDICAL SCIENCE

CALGARY, ALBERTA

JULY, 2019

Abstract

Background: Major trauma is associated with high incidence of septic complications and multiple organ dysfunction (MOD). We assessed the prognostic value of serum and peritoneal procalcitonin (PCT) levels after trauma.

Methods: We searched electronic database and included original studies that assessed prognostic value of PCT after trauma. We performed a retrospective analysis of the Intraperitoneal Vacuum Trial to assess correlation of plasma and peritoneal levels of PCT with clinical outcomes in patients managed with the open abdomen (OA) technique

Results: Among 2,015 citations identified, 19 studies met inclusion criteria. All studies showed a strong correlation between initial PCT levels and Injury Severity Score (ISS). Initial peak PCT levels predicted development of sepsis and MOD after trauma.

Conclusion: PCT seems to hold promise as a surrogate biomarker for trauma. Initial peak PCT level may be used as an early predictor of sepsis, MOD, and mortality in trauma population.

Contribution of Authors

Dr. Fatma Al Hinai- Co-author in all written manuscripts, acted as secondary reviewer for both manuscripts, reviewed all titles, abstracts and full-text articles for systematic review, performed secondary data extraction and quality assessment, reviewed and discussed results, edited and reviewed final manuscripts.

Dr. Andrew Kirkpatrick- Co-author in all written manuscripts, primary investigator for second manuscript, provided concept of project, reviewed and aided in results analysis, edited and reviewed final manuscript

Dr. Christopher Doig- Co-author in all written manuscripts, provided support for systematic review, reviewed study protocol, reviewed results, edited and reviewed final manuscripts

Dr. Call Ball- Co-author in all written manuscripts, aided in conceptualization of project, reviewed results, edited and reviewed final manuscripts

Dr. Elijah Dixon- Co-author in all written manuscripts, aided in conceptualization of project, reviewed results, edited and reviewed final manuscripts

Zhengwen Xiao- Co-author in the first manuscript, performed initial consensus review, provided feedback, reviewed final manuscript

Acknowledgements

I would like to thank my thesis advisors Dr. Andrew Kirkpatrick and Dr. Christopher Doig for their continuous support, patience, motivation and guidance throughout my years of Master study. Their office doors were always open whenever I had a question about my project or ran into a trouble

I thank my supervisory committee for their expertise, encouragement and support

I would also like to acknowledge Dr. John Kortbeek for his insightful motivational and life chats

Many Thanks to my friend Fatma Al Hinai for her support, encouragement, the sleepless night we spent working together and all the fun we had so far

Finally, I must express my very profound gratitude to my super amazing parents and siblings (Manal, Maisa, Hamood & Areen) for providing me with continuous support and encouragement throughout my years of study and writing this thesis. This accomplishment would not have been possible without them

Dedication

To my parents, without whom none of my success would be possible. Thank you for inspiring me to keep going.

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List of Symbols, Abbreviations and Nomenclature

Symbol	Definition
ACS	Abdominal Compartment Syndrome
ANPPT	Active Negative Pressure Peritoneal Therapy
APATCHE	Acute Physiology And Chronic Health Evaluation
BVP	Barker's Vacuum Pack
CRP	C-Reactive Protein
ELFA	Enzyme-Linked Fluorescent Immunoassay
HAI	Hospital Acquired Pneumonia
IAH	Intra-Abdominal Hypertension
ICU	Intensive Care Unit
IL	Interleukin
ISS	Injury Severity Score
IQR	Interquartile Ranges
MDA	Malondialdehyde
MMRM	Mixed Model for Repeated Measures
MOD	Multiple Organ Dysfunction
MODS	Multiple Organ Dysfunction Syndrome
MOF	Multiple Organ Failure
NPWT	Negative Pressure Wound Therapy
NT	Neopetrin
OA	Open Abdomen
OR	Odd Ratio
PCT	Procalcitonin
PMN	Polymorphonuclear leucocyte
PRISMA	Preferred Reporting Item for Systematic Reviews and Meta-Analysis
PSP	Pancreatic Stone Protein
QUIPS	Quality in Prognosis Studies
SD	Standard Deviation
SIRS	Systemic Inflammatory Response Syndrome
SOFA	Sequential Organ Failure Assessment
TAC	Temporary Abdominal Closure
TNF-α	Tumor Necrosis Factor-Alpha

Epigraph

"You can never solve a problem on the level on which it was created"

-Albert Einstein

Chapter One: **Introduction**

Abdominal trauma and intra-abdominal sepsis are associated with significant morbidity and mortality.[1, 2] Microcirculation in the gut is disrupted in hemorrhagic and septic shock leading to tissue hypoxia, disruption of barrier integrity, increased mucosal permeability, release of pro-inflammatory mediators and ascites formation. The damaged gut acts as reservoir rich in inflammatory mediators and provides a continual source of inflammation to the systemic circulation and is likely the initial motor of multiple organ dysfunction (MOD).[3,4] Damage control laparotomy followed by temporary abdominal closure (TAC) and planned reoperation has been increasingly used among severely injured or critically ill patients in attempt to control ongoing hemorrhage or peritoneal soilage contributing to these physiological derangements prior to completing a definitive repair. Its use, however, remains controversial given its potential side effects.

Recent evidence suggests that TAC technique may play a role in patient outcomes.[5,6] In theory, TAC techniques that employ negative pressure to the abdominal cavity may remove inflammatory ascites rich in cytokines. This would cause a moderation of systemic inflammation and prevent organ damage. However, little clinical data exist to support superiority of one TAC technique over another.

Animal studies have shown that active removal of cytokine-rich pro-inflammatory peritoneal fluid from the open abdomen mitigated the systematic inflammatory response and improved cardiac, pulmonary, gastrointestinal and renal function. In addition, TAC via active negative pressure led to increased survival compared to passive drainage.[4]

Human studies have demonstrated that use of negative pressure wound therapy (NPWT)

improved survival and primary fascial closure rates among critically ill or injured patients when compared to an alternate type of TAC technique.[5,6] These studies postulated that removing peritoneal inflammatory fluid by NPWT was the likely mechanism of protection.

The Intraperitoneal Vacuum Randomized Controlled Trial has reported improved survival among critically ill or injured patients randomized to the ABThera Open Abdomen Negative Pressure Therapy device when compared to a more passive TAC (Barker's vacuum pack- BVP) for open abdomen management after abdominal injury or intra-abdominal sepsis.[8] However, improvement in survival did not appear to be mediated by an improvement in peritoneal fluid drainage or reduced markers of systemic inflammation that have been studied. The study manipulated peritoneal fluid and plasma concentrations of the pro-inflammatory cytokines IL-6, IL-1β, IL-8, IL-10, IL-12 p70 and TNF-α to determine the effect of negative pressure peritoneal therapy on the inflammatory response after damage control laparotomy. However, there was no difference in cytokines concentration at 24 or 48 hours versus baseline between patients randomized to the ABThera versus Barker's vacuum pack. To gain further insight into this complex immune response after damage control laparotomy, we sought to assess other inflammatory mediators that may play a role in improving clinical outcomes.

Procalcitonin levels (PCT) have recently emerged as a promising biomarker in the management of sepsis. PCT is a 116-amino acid polypeptide precursor of calcitonin produced by the C-cells of the thyroid gland. In response to bacterial endotoxins or pro-inflammatory cytokines such as Interlukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), various extrathyroidal tissues produce PCT, resulting in up to 1000-fold increase in levels.[9,10] PCT levels are closely related to the severity of systemic inflammation, with higher levels associated with severe sepsis and potentially most importantly, declining levels are associated with the resolution of

infection.[11]Given these unique characteristics and reliable kinetics, PCT measurements have been suggested to be superior to previously studied biomarkers for use in the diagnosis of sepsis, monitoring sepsis course and severity, and guiding antimicrobial therapy.[12,13]

1.1 Objectives of the study

The aim of this project is to add more understanding of the role of the biomarker PCT in predicting clinical outcomes in critically ill/injured patients. We will conduct a systematic review and meta-analysis (if applicable) to evaluate the prognostic role of PCT in predicting severity of injury, sepsis, organ dysfunction and mortality among critically injured patients. We then will study PCT levels in a defined well studied population of critically ill/injured patients who required open abdomen management with TAC technique

The primary objective is to determine if the use of ABThera, an active negative peritoneal pressure dressing, reduces the extent of systematic inflammatory response after damage control laparotomy when compared to Barker's vacuum pack by examining serum and peritoneal levels of PCT. The secondary objective is to evaluate PCT measurements as predictors of mortality in patients managed with the open abdomen technique.

1.2 Material & method

1.2.1 Assess PCT levels after severe illness/injury necessitating open abdomen management with TAC

I will test the hypothesis that ABThera reduces the extent of systemic inflammatory after damage control laparotomy for intra-abdominal sepsis or injury as compared to Barker's vacuum pack, which provides potentially less efficient peritoneal drainage.

Primary endpoint is the difference in the peritoneal and plasma concentration of PCT at 24 and 48 hours after TAC application between patients randomized to ABThera versus Barker's vacuum pack after damage control laparotomy for intra-abdominal sepsis or injury.

1.2.2 Assess the predictive value of PCT for survival and disease severity in critically ill/injured adults managed with the open abdomen technique

Secondary endpoint is the relation of median PCT levels with injury/illness severity and 30-day mortality

This will be a retrospective analysis of data obtained from a single center randomized control trial conducted at the Foothills Medical Center in Calgary.[8] The study sample included forty-five patients with abdominal injury or intra-abdominal sepsis randomly allocated to the ABThera (n = 23) or Barker's vacuum pack (n = 22) after damage control laparotomy. Patients younger than 18 years and those who were pregnant or received intraperitoneal chemotherapy were excluded from the trial. Blood and peritoneal fluid samples were collected from all patients at baseline (before TAC application) and at 24 and 48 hours after TAC application. Plasma and peritoneal fluid concentration of PCT were determined using Luminex technology. Clinical data on patient demographics; age, indication for damage control laparotomy, sequential organ failure assessment (SOFA) scores, Acute Physiology and Chronic Health Evaluation (APATCHE-II) and 30-day mortality will be used in the analysis.

1.3 Statistical analysis

Data were summarized using mean ± standard deviation (SD) and median with interquartile ranges (IQR) for normally distributed and skewed data respectively. Between groups comparisons were performed by either Wilcoxon rank-sum test or Student's t test (depending on data distribution) for continuous data, or by Fisher's exact test for categorical data.

For primary endpoint, data on PCT measurements will be log transformed as they had strongly skewed distribution. Difference in PCT measurements between treatment arms at 24 and 48 hours after TAC application will be compared using Mixed model for repeated measures analysis (MMRM).[14] MMRM will also be used to compare PCT levels between survivors and non-survivors at different time points. Multivariable logistic regression model will be used to calculate odd ratio (OR) for 30-day mortality. Models will include baseline variables to adjust for any differences between groups including baseline values of PCT, age, gender, SOFA score, APACHE II score, Injury Severity Score (ISS) for trauma patients, and Charlson Comorbidity Index. A p-value of less than 0.05 will be considered significant. Stata version 13.0 (Stata Corp., College Station, TX, USA) will be used for all analyses.

1.4 Anticipated outcomes and significance

The project will help further address the mechanism whereby ABThera improves clinical outcomes and determine the clinical utility of PCT levels after damage control laparotomy for abdominal trauma and intra-abdominal sepsis.

Chapter Two: **The Prognostic Value of Serum Procalcitonin Measurements in Critically Injured Patients: A Systematic Review**

2.1 Abstract

2.1.1 Background

Major trauma is associated with high incidence of septic complications and multiple organ dysfunction (MOD), which markedly influence the outcome of injured patients. Early identification of patients at risk of developing posttraumatic complications is crucial to provide early treatment and improve outcomes. We sought to evaluate the prognostic value of serum procalcitonin (PCT) levels after trauma as related to severity of injury, sepsis, organ dysfunction and mortality.

2.1.2 Methods

We searched PubMed, MEDLINE, EMBASE, the Cochrane Database and references of included articles. Two investigators independently identified eligible studies and extracted data. We included original studies that assessed prognostic value of PCT after trauma.

2.1.3 Results

Among 2,015 citations, 19 studies (17 prospective; 2 retrospective) met inclusion criteria. Methodological quality of included studies was moderate. All studies showed a strong correlation between initial PCT levels and Injury Severity Score (ISS). Twelve out of sixteen studies demonstrated significant elevation of initial PCT levels in patients who later developed sepsis after trauma. PCT level appeared a strong predictor of MOD in 7 studies out of 9. While two studies did not show association between PCT levels and mortality, four studies demonstrated significant elevation of PCT levels in non-survivors versus survivors. One study reported that PCT level of

≥5 ng/mL was associated with significantly increased mortality (OR 3.65; 95% CI: 1.03-12.9; p=0.04)

2.1.4 Conclusion

PCT seems to hold promise as a surrogate biomarker for trauma. Initial peak PCT level may be used as an early predictor of sepsis, MOD, and mortality in trauma population.

2.1.5 Key Words

Procalcitonin, Prognosis, Trauma, Injuries, Critical Care, Intensive Care Unit

2.2 Background

Trauma is the leading cause of death during the first 4 decades of life and the third leading cause of death overall, across all age groups.[15,16] Each year trauma accounts for 41 million emergency department visits and 2.3 million hospital admissions in the United States, of these 192,000 die as a result of their injuries.[16] The triphasic peaks of death after injury have long been described epidemiologically. Essentially catastrophic non-survivable injuries occur at the time of injury, with subsequent airway obstruction, respiratory failure, and especially hemorrhage predominating as the second peak. The recognition of non-recoverable head injury and especially sepsis/ systemic inflammatory response syndrome (SIRS) related deaths constitute the third.[17,18] Although the global burden of traumatic death is ominous in its predicted future increase as the developing world mechanizes, great strides have recently been made in addressing both the primary peak with injury prevention and safety conscious designs, and in the 2nd peak related to dramatic advances in resuscitation for hemorrhage among other interventions.[19,20] Progress in improving the outcomes of post-traumatic sepsis/SIRS is urgently required though. Sepsis remains a major challenge in critically injured patients with an incidence ranges between 2% and 17% during posttraumatic period, with associated mortality rates reaching as high as 23%.[21]

Major trauma provokes a strong systemic inflammatory response syndrome (SIRS) early after traumatic injury as a result of tissue damage, hypotension, hypoxia, cytokines release, and inflammation.[22] The prognosis is strongly related to the posttraumatic balance between pro and anti-inflammatory responses. [23-26] Following this induction of the inflammatory cascade follows an increase in counter regulatory anti-inflammatory cytokines, which subsequently result in immunosuppression and increase susceptibility to infection and complications such as sepsis. Together, the consequence of initial injury and inflammation, subsequent immune suppression and

infection, results in MOD/MOF. [23,26] Multiple organ dysfunction (MOD) or multiple organ failure (MOF) unfortunately remains the leading cause of late death following trauma.[27]

Early identification of patients at risk of developing posttraumatic complications is crucial to allow the provision of early and appropriate therapy for sepsis. It has been demonstrated that prompt and appropriate management of sepsis prevents MOD, reduces mortality and improves clinical outcomes.[28,29] Thus any test or clinical information that facilitates an earlier diagnosis or safely triggers the earlier appropriate treatment of sepsis may save lives. Past research has explored a number of some inflammatory markers for their prognostic value but no clear message regarding what if any marker to rely on has emerged, despite promise.[30-32]

This is especially true with regards to measurement of serum procalcitonin (PCT) levels, which has been of recent interest as a potential and more accurate marker of sepsis in critically ill patients. PCT is a 116-amino acid polypeptide precursor of calcitonin produced by the C-cells of the thyroid gland. Healthy individuals typically have serum PCT levels less than 0.05 ng/ml. In response to bacterial endotoxins or pro-inflammatory cytokines such as Interlukin-6 (IL-6) and tumor necrosis factor alpha (TNFα), various cell types outside the thyroid gland produce PCT, resulting in up to 1000-fold increase in levels.[9,10] These PCT increases occur with severe inflammation, including systemic infection and especially severe sepsis.[33-35] PCT levels are thus closely related to the severity of systemic inflammation, with higher levels associated with severe sepsis and potentially most importantly, declining levels are associated with the resolution of infection.[11] Given these unique characteristics and reliable kinetics, PCT level has emerged as a promising biomarker. Therefore, it has been suggested that serum PCT level determination may be superior to previously studied biomarkers for use in the diagnosis of sepsis, monitoring sepsis course and guiding antimicrobial therapy.[30,32,12,13,36]

However, in heterogeneous populations of critically ill patients the results concerning PCT performance in prognosis and correlation with outcomes remain conflicting. In this review therefore, we attempt to extend the scope of previous reviews by evaluating the prognostic value of serum PCT levels, in a more homogenous group of critically injured adult patients, as related to severity of injury, sepsis, organ dysfunction and mortality.

2.3 Materials and Methods

2.3.1 Search Strategy

A systematic literature search was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Group[37] using the following databases from their inception to September 2018; PubMed, Ovid MEDLINE, EMBASE, and the Cochrane Library. Medical Subject Heading terms and keywords for procalcitonin, trauma, injury, prognosis and predictive value were used. The search was limited to original studies on human subjects, published in English language. To identify other potentially relevant articles, the PubMed "related articles" feature was utilized and the two authors (A. R. and F. H.) independently hand-searched the reference list of included articles and relevant reviews for additional citations.

2.3.2 Study selection

Two reviewers (A. R. and F. H.) independently screened the titles and abstracts of all identified citations for potential eligibility. The following inclusion criteria were applied: (1) study participants (adults ≥16 years old trauma patients); (2) intervention (single or serial measurements of serum procalcitonin level from day of admission to trauma center or Intensive Care Unit (ICU) following trauma); (3) comparison of prognostic performance of PCT levels compared to other

potential biomarkers; (4) outcome (documentation of at least one of the outcomes of: sepsis, organ dysfunction, mortality, or correlation of PCT with severity of injury) (5) cohort or case-control study design.

Reviews, case reports, letters, conference abstracts and editorials were excluded. Articles involving isolated injury to the central nervous system and pediatric or burn trauma were also excluded. Full-text articles of identified abstracts that were relevant with the inclusion criteria were assessed for final eligibility. The agreement between the two reviewers was assessed using Kappa statistic for the inter-rater reliability.[38]

2.3.3 Data Extraction

Two reviewers (A. R. and F. H.) independently extracted data using a standardized recording tool to record the study design and setting, year of publication, country of origin, number of study participants, participant clinical characteristics, PCT testing system, kinetics of PCT, markers other than PCT, and study outcomes.

We defined the terms "SIRS" and "Sepsis" according to the American College of Chest Physician/Society for Critical Care Medicine,[39] which supported definition of SIRS, sepsis and severe sepsis as most studies were published prior to the release of Sepsis-3.[40]

2.4 Methodological quality assessment

The risk of bias of the included studies was assessed by two independent investigators (A. R., F. H.) using the Quality in Prognosis Studies (QUIPS) tool developed by Hayden et al.[41] This tool consists of 30 criteria divided into six domains of; patient selection, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, statistical

analysis and reporting. Each criterion was scored using "yes", "no" or "unclear". This scoring led to the overall judgment of "low", "moderate" or "high" risk of bias per domain. We considered a study to be of high quality when the bias was rated as low or moderate with respect to almost all of the domains. Conversely, a study was considered to be of low quality when the bias was rated high in most of the bias domains. Disagreements were resolved by consensus.

2.5 Results

2.5.1 Literature Search:

Figure 1. presents a flow diagram of study identification and subsequent inclusion. Among 2,015 citations identified by the search, 19 studies fitted the inclusion criteria including 4,146 patients with multiple trauma. There was an excellent inter-investigator agreement on the inclusion of full-text articles in the systematic review (κ statistic=0.88; 95% CI=0.65-1.00).

Due to heterogeneity between studies with respect to definition of clinical outcomes and statistical methods, it was not possible to statistically pool the results. Instead, findings were reported descriptively.

2.5.2 Characteristics of the Included Studies:

Table 1. details the characteristics of the included studies. The included studies were published from 1998 to 2016, while the majority were published after 2006 (13/19; 68.4%). Sixteen studies were conducted in Europe[43,46-60] (84.2%), two were conducted in Asia [42,44] (10.5%) and one was conducted in the United States[45] (5.2%). Eleven studies were prospective cohort, [43,45-48,50-52,54,55,60] six studies were prospective case control,[42,44,53,56-58] one study was retrospective cohort study[49] and one study was retrospective case control.[59]

Twelve studies (63.3%) were conducted in the critical care units.[44-46,48,49,51-54,57,59,60] Overall, the aggregate study population included a total of 4,146 patients with trauma in whom serum PCT levels were used to predict posttraumatic complications. The mean age ranged between 34 to 49 years. The mean injury severity score ranged from 21 to 32. The mechanism of injury was blunt and/or penetrating trauma. All studies were civilian, with none comprising military populations or combat injuries.

2.5.3 Risk of Bias Assessment:

Table 2. summarizes the risk of bias assessment for all included studies. Most studies were assessed to be of low to moderate risk of bias. Nine studies demonstrated high risk of bias in at least one domain.[42-44,46,48,50,51,53,55] Study confounding domain was deemed to be at moderate to high risk of bias in 14 studies (73.7%).[42-55,46-55,60] The majority did not account for potential confounding factors in the study designs and/or made adjustment for the effects of the confounders in the analysis, while 21.1% of these studies did not name any confounder.[44,52,53,55] The risk of bias was moderate to high to in the domain of statistical analysis in 10 studies (52.6%).[42-44,46,48,50,51,53,55,60] Only 7 studies used statistical models to assess prognostic relationships.[45,46,49,50,51,54,56] In one study, mortality data were presented in graph only.[43]

2.5.4 Kinetics of PCT

PCT levels were measured from the serum sample in all studies, using immunoluminometric assay (LUMItest) in 11 studies (57.8%)[47,49,51-54,56-60] and Kryptor Assay in 3 studies (15.7%).[45,46,50] Other techniques used to determine PCT levels were Roche Cobas e 411,[42] VIDAS system,[44] enzyme-linked fluorescent immunoassay (ELFA)[43] and chemiluminescence

analyzer.[48] Most studies showed rapid kinetics of PCT levels with peak levels reached on day one post trauma, [42,45,47-52,54,56-60] and to a lesser extent on day two.[43,46] PCT levels declined rapidly thereafter towards the normal range. Sakran et al.[45] and Haasper et al.[46] demonstrated that a biphasic rise in PCT after day seven was associated with development of sepsis.

2.5.5 Correlation between PCT levels and injury severity and injury pattern

Nine studies (47.4%) [42,48,50,51,54-56,59,60] assessed the correlation between initial PCT level and the severity of injury using Injury Severity Score (ISS).[61] All studies showed a correlation between initial PCT levels and ISS. When patients were categorized into those with severe trauma (ISS>20) or moderate trauma (ISS<20), the initial PCT was significantly higher in patients with severe trauma.[50,51,54,59]

Four studies assessed the association between PCT level and injury pattern, three of which showed that serum levels of PCT were higher among patients with abdominal injury,[44,50,54] whereas one study showed no correlation between PCT level and injury pattern.[59]

2.5.6 The value of serum PCT levels in differentiating sepsis from non-infectious systemic inflammation in injured patients

Sixteen studies (84.2%) assessed the utility of serum PCT level as a marker for sepsis.[42,44-49,51-59] In patients who developed systemic or septic complications, the kinetic of PCT was similar to those without complications. After reaching the peak level on day 1 after trauma, an immediate decline was observed towards normal range.[45,47,49,54,59] However, the initial peak PCT was significantly higher in patients who subsequently developed sepsis compared to those without sepsis and difference remained significant between the two groups during the study period.[42,45,47-

[49,50,54,55,58,59] Further, patients who developed sepsis demonstrated a significant increase of peak PCT levels compared with patients with noninfectious systemic inflammation.[54,51,52,59] Warner et al. demonstrated a 3.9 fold increase of initial peak PCT levels in injured patients with sepsis compared with patients with SIRS. [59] Castelli et al. observed a significant increase in PCT level in trauma patients at day of sepsis diagnosis as compared with levels measured on day one before the diagnosis. [48] Rajkumari et al. reported that all patients with serum PCT level >2ng/ml developed infections after trauma. [44]

The most common identified sources of infection resulting in sepsis were the lungs,[45,48,49,51,52,54,57,59] bloodstream,[45,48,49,51,52,54] urinary tract infection,[45,48,49,54,57] soft tissue infection,[48,51,52,54,57,59] peritonitis,[48,52,54,59] and bacterial meningitis.[42,59] However, four studies reported no significant difference in PCT level between patients who developed sepsis and those who did not,[46,53,56,57] although one study evaluated the predictive value of PCT level for the development of posttraumatic pneumonia and reported higher PCT levels among patients who developed pneumonia compared with those without, but the difference did not reach significance.[53]

2.5.7 The value of serum PCT levels in predicting the future occurrence of MODS in injured patients

Nine studies (47.4%) assessed the utility of serum PCT level in predicting the future occurrence of MOD and/or MOF in injured patients.[44,46,48,52,54,56,58-60] Studies used either the Sequential Organ Failure Assessment (SOFA)[62] or the Multiple Organ Failure Score developed by Goris to assess the severity of organ dysfunction.[63,64] Seven studies demonstrated significantly higher initial PCT levels in patients who subsequently developed MODS compared to those patients without MODS.[46,48,52,56,58-60] Haasper et al. observed elevated PCT level preceding the

development of MODS by 3 days. [46] Hensler et al. divided patients with MOF into early and late MOF using day 3 as cut-off point to avoid biased results by patients who developed MOF already on day 1. Results remained significant for both groups when compared with patients without MOF. [56] However, two studies showed no correlation between PCT levels and severity of organ dysfunction. [44,54]

2.5.8 The value of serum PCT levels in predicting mortality in injured patients

Among seven studies assessed the value of procalcitonin serum level determination in predicting death following trauma, three studies demonstrated significant elevation of PCT levels in non-survivors compared with that in survivors.[43,51,54] The difference in PCT level between the two groups remained significant during the first week after trauma in two of those studies.[51,54] Meisner et al. showed that by the end of the first week the difference between survivors and non-survivors increased up to 15 fold in patients with fatal outcome. [54] A study by Sakran et al. demonstrated significantly increased mortality among patients with a PCT level of ≥5ng/ml compared with that of patients with less than 5ng/ml, with odds ratio of 3.65; 95% CI: 1.23-4.61, p=0.01). [45] Conversely, two studies reported no association between PCT level and fatal outcome.[56,59]

2.5.9 Prognostic value performance of PCT levels compared to other potential biomarkers

Fourteen studies (73.7%) assessed serum PCT levels and other biomarkers simultaneously to predict posttraumatic complications (Table 3). Five studies demonstrated slow induction of C-Reactive Protein (CRP) after trauma with peak levels reaching on day 3 after trauma.[47-49,52,54] PCT was superior to CRP in predicting septic complications in these studies.

Interleukin 6 (IL-6) has a similar kinetics to those of PCT. IL-6 increases during the early phase after trauma with peak levels reached on day 0 after trauma.[46,47,49,58] While Billeter et al. observed a significant difference in IL-6 levels between patients who developed sepsis and those who did not on day 3 & 5 after trauma, [49] Keel et al observed this difference only after day 5. [47] Haasper et al demonstrated low sensitivity of IL-6 for predicting sepsis and low specificity for predicting both sepsis and MODS. [46]

2.6 Discussion

Serious traumatic injuries often induce overwhelming systemic inflammation that can disrupt immune system homeostasis and predispose patients to septic complications with an ultimately fatal outcome. Ongoing international efforts have produced substantial progress into understanding how trauma affects the immune system, although the overall picture is confusing and still in its relative infancy. Nonetheless, irrespective of the exact molecular mechanisms involved it remains true that the basic principle of initiating appropriate antibiotics early while searching for and correcting the source of septic complications will save lives.[65] However, the indiscriminate use of broad spectrum antibiotics based on the mere chance that a patient may be developing sepsis cannot be justified, and such practices have grave implications for all the critically ill/injured in the future. Thus, a biomarker that may help identify patients who are either developing or at high risk for developing sepsis before this becomes otherwise clinically apparent might ameliorate such adverse outcomes following trauma.

Since its first description in 1993 by Assicot et al authors have described a strong and generally consistent association between serum PCT level the subsequent clinical course of severely traumatized patients. [11] Early elevation of PCT is related to the severity of trauma and

magnitude of tissue injury. Trauma patients with SIRS may have initially high levels of PCT, which may overlap with sepsis. However, a very high induction of PCT and/or sustained elevation correlates with a substantially increased risk for septic complications. Moreover, rapid decline to normal levels most often indicates resolution of systemic inflammation and/or infection. Therefore, under these circumstances the initial peak PCT level can reliably differentiate between infectious and non-infectious SIRS in critically ill and hence outperform other biomarkers such as C-reactive protein and IL-6.[66,67] Since the increase in PCT level usually precedes the onset of clinical symptoms, it allows earlier detection of infection than the conventional standard methods.

In our review, four studies did not demonstrate an association between PCT level and development of sepsis. The variability in the results might be related to the lack of consistency in defining sepsis and lack of consensus gold standard for defining infection per se. This could have misclassified patients as having SIRS if potentially infected patients did not exhibit clinical signs or in whom bacterial cultures were negative.

Sepsis and MOF are the predominant cause of late death in trauma .[27] A review by Ciriello et al. reported the usefulness of PCT level in predicting sepsis course in trauma population, thus allowing early diagnosis of MODS. [32] Our review suggests there is also utility of PCT level in predicting mortality. In this group of patients, early recognition of septic complications through the use of a specific and rapid marker for infection, and hence early therapeutic decision may have an impact on survival and improve outcomes. In our reviews, most studies demonstrated a significant increase in early PCT level in non-survivors compared with that in survivors after trauma. Two studies did not show an association between PCT level and late mortality. In the study of Wanner et al. the incidence of sepsis was low (11.1%) and 70% of the deaths occurred in less than 72 hours after trauma. [59] In the study of Hensler et al. a small number of patients died after

trauma. [56] Furthermore, the time frames in the definition of mortality varied across studies; some studies used ICU mortality, whereas other studies used 28-day mortality. These limitations could probably preclude achieving a substantial difference. Nevertheless, sepsis is clearly associated with high mortality. Studies have found that the mortality from trauma related sepsis is significantly higher than mortality from trauma alone.[68,69] PCT has been shown to reflect the prognosis of sepsis in septic patients. Svoboda et al. observed a tendency to reduce mortality rate in septic patients after multiple trauma or major surgery using PCT in guiding early re-intervention.[70]

To our knowledge, this is the first systematic review to comprehensively assess the prognostic value of PCT level in relation to four outcomes including severity of injury, development of sepsis and MODS, and mortality in trauma patients. Most studies in our review were prospective, which allowed the study of the kinetics of PCT level from day 0 post trauma, and its association with the occurrence of complications later in the subsequent clinical course, hence accurately assessing the prognostic value of PCT level.

This review has several limitations. We did not include non-English publications in our review. The quality of the primary studies varied with main issue related to confounding variables. Statistical methods used in outcomes assessment varied across studies making combining results in a meta-analysis difficult which certainly represent a drawback of the current review. There was lack of a consensus definition of the term severe trauma. This could induce a high heterogeneity among trauma patients due to variations in the immunological responses depending on the injury pattern

2.7 Conclusions

Despite the limitations identified during this review, PCT seems to hold promise as a surrogate biomarker for trauma. Initial peak PCT level may be used as an early predictor of severity of injury, development of sepsis and MOD, and mortality in trauma population. Serum PCT levels may contribute to the identification of patients who may benefit most from more aggressive management. However, further studies, preferably randomized trials (to control confounding factors and selection bias) are necessary to confirm these findings.

Chapter Three: **Intra-peritoneal procalcitonin levels but not plasma may correlate with clinical outcomes in critically ill/injured adults managed with the open abdomen technique: A retrospective analysis of the Intraperitoneal Vacuum Trial**

3.1 Abstract

3.1.1 Background

Temporary abdominal closure (TAC) techniques are necessitated by selection of the open abdomen after abbreviated laparotomy. TAC with active negative pressure peritoneal therapy (ANPPT) has been associated with improved outcomes, potentially by more effectively removing cytokine-rich peritoneal fluid and hence reducing the systematic inflammatory response. As the mechanism of ANPPT benefit remains unknown and procalcitonin (PCT) is a potentially promising biomarker/biomediator, this study explored the associations and behavior of PCT levels after severe illness/injury necessitating open abdomen and TAC.

3.1.2 Methods

PCT levels (plasma and peritoneal fluid) were measured among 45 subjects randomized to ANPPT or a more passive TAC (Barker's vacuum pack - BVP) for open abdomen management after abdominal injury or intra-abdominal sepsis. The primary end-point was PCT level differences at 24 and 48 hours after TAC application. The secondary end-point correlated PCT levels with mortality.

3.1.3 Results

Forty enrolled patients completed >24 hours of allocated TAC therapy. There were no differences in PCT plasma levels between groups at 24 ($p=0.40$) or 48 hours ($p=0.54$). However, there was a

significant difference in the PCT peritoneal levels at 24 hours (p=0.004) between ANPPT versus BVP. While 30-day mortality was 13% for ANPPT and 45% for BVP (p=0.02) patients, there was no significant difference in the plasma PCT levels between survivors and non-survivors at 24 and 48 hours after baseline at enrollment (p=0.32, 0.12 respectively).

3.1.4 Conclusions

ANPPT may induce a lower inflammatory response after abbreviated laparotomy. While open abdomen management with ANPPT associated with increased survival compared to BVP, manipulation of serum procalcitonin levels was not apparent.

3.1.5 Funding:

No funding was provided for this analysis and manuscript. Funding for the original Peritoneal VAC study was provided by the Department of Surgery, University of Calgary, Surgical Research Fund and an unrestricted grant from the Acelity Corporation, San Antonio, Texas.

3.1.6 Keywords

inflammation, injury, biomarkers, Procalcitonin, open abdomen, abbreviated laparotomy, negative pressure wound therapy, temporary abdominal closure.

3.2 Introduction

Severe intra-peritoneal sepsis is one of the most challenging situations in surgery with a continuously increasing incidence and a mortality rate ranging from 30% to 80%.[71,72] Deciding to leave the midline abdominal fascia "open" after a laparotomy is a non-anatomical technique associated with improved outcomes in catastrophic situations that is used to expedite and/or facilitate future re-laparotomy. [73-75] This Open Abdomen (OA) technique is increasingly used among severely injured or critically ill patients in attempt to control ongoing hemorrhage or contamination prior to completing a definitive repair.[76] In the interval between the index abbreviated laparotomy and subsequent definitive closure, a temporary abdominal closure (TAC) is required to protect the viscera and to conserve fluids and heat. Recently, specialized TAC devices utilizing active negative peritoneal pressure therapy (ANPPT) which may facilitate more efficient drainage of peritoneal fluid have been associated with improved outcomes in the management of OA.[5,8,77,78]

Evidence suggesting dramatic benefits of ANPPT have included basic animal research.[4,79,80] and uncontrolled prospective clinical series.[75] The Intraperitoneal Vacuum Randomized Controlled Trial recently reported significantly improved survival among critically ill/injured patients randomized to ANPPT using the ABThera™ Open Abdomen Negative Pressure Therapy device when compared to a more passive technique (Barker's vacuum pack technique-BVP) for OA management after abdominal injury or intra-abdominal sepsis. However, the improvement in survival was not explained through either improvement in peritoneal fluid drainage or reduction in a panel of standard biomarkers (IL-1β, -6, -8, and -12, and tumor necrosis factor–α (TNF-α)) of systemic inflammation that were studied.[8] Thus, while OA management with ABThera™ OA NPT associated with increased survival the exact mechanism is unclear.

A growing body of evidence supports the use of procalcitonin (PCT) in the diagnosis of sepsis, monitoring sepsis course and severity, and guiding antimicrobial therapy in the critically ill patients.[12,13,36,81,82] PCT is a pro-hormone of calcitonin that is produced mainly by thyroid cells. During inflammation and or sepsis, PCT is produced by various extra-thyroidal neuroendocrine tissues, resulting in up to 1000-fold increase in levels.[9] While serum PCT levels correlate with severity of the illness, declining levels are associated with resolution of the systemic inflammation or infection which makes it an ideal biomarker in understanding progression and regression of the systemic illness, and outcomes of the treatment regimens.

In order to explore whether selective manipulation of procalcitonin levels through ANPPT might be related in improved clinical outcomes, PCT levels were specifically examined in this study. Thus, the primary objective of this study was to determine if the use of ANPPT reduced the extent of systematic inflammatory response after abbreviated laparotomy when compared to BVP by examining PCT levels in critically ill/injured patients who required OA management with TAC technique. The secondary objective was to evaluate correlation of PCT levels with mortality in patients managed with the OA techniques.

3.3 Methods

This is a novel retrospective analysis of data from a single center, parallel-group randomized controlled trial conducted between September 2011 and December 2012 at the Foothills Medical Center, level 1 trauma center in Calgary, Alberta, Canada. Forty-five patients with intra-abdominal injury or intra-abdominal sepsis who required TAC following abbreviated laparotomy were intra-operatively randomized to receive either an ANPPT (n=23) or BVP (n=22) TAC device. Methods describing allocation concealment and randomization, study intervention,

and collection and analysis of blood and peritoneal samples were previously reported in detail.[8,83] Patients younger than 18 years and those who were pregnant or had received intra-peritoneal chemotherapy were excluded from the study. Patient characteristics, clinical, laboratory, and mortality results of patients in both groups were recorded prospectively and analyzed retrospectively. The study was approved by the Conjoint Health Research Ethics Board (CHREB) at the University of Calgary.

3.3.1 Study Endpoints:

The primary end-point was the difference in the plasma and peritoneal fluid levels of PCT at 24 and 48 hours, and 1 week after TAC application between patients randomized to the ANPPT versus BVP after abbreviated laparotomy in those who completed at least 24hours of the allocated therapy. Secondary end-points were related to the correlation of plasma and peritoneal PCT kinetics with 30-day mortality outcome. Both the primary and secondary endpoint measures were further analyzed according to the etiology of the patients with open abdomen (intra-abdominal injury versus intra-abdominal sepsis)

3.4 Statistical analysis:

Data were summarized using mean ± standard deviation (SD) and median with interquartile ranges (IQR) for normally distributed and skewed data respectively. Between groups comparisons were performed by either Wilcoxon rank-sum test or Student's t test (depending on data distribution) for continuous data, or by Fisher's exact test for categorical data. Logarithmic transformation of PCT levels was used for the analyses. Mixed model for repeated measures analysis (MMRM) was used to compare the effects of ANPPT and BVP on

levels of PCT at 24, 48 hours and 1 week after TAC application.[84] MMRM was also used to compare PCT levels between survivors and non-survivors at different time points. We assumed missing at random assumption (subjects would have completed the study as like completers if death or dropout did not occur) for accounting the missing data. Multivariable logistic regression model was used to calculate odd ratio (OR) for 30-day mortality. Models included baseline variables to adjust for any differences between groups including baseline values of PCT, age, gender, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, Injury Severity Score (ISS) for trauma patients, and Charlson Comorbidity Index. A p-value of less than 0.05 was considered significant. Stata version 13.0 (Stata Corp., College Station, TX, USA) was used for all analyses.

3.5 Results

3.5.1 Patient characteristics:

The baseline characteristics and severity of illness of the ANPPT and BVP groups are described in **Table 4**. Out of 45 patients enrolled (23 ANPPT; 22 BVP), only 40 completed at least 24 hours of the allocated TAC therapy because of fatal outcomes within 24 hours. The median age was 56 years (range, 34-68 years; 37 male patients; 8 female patients). The indication for abbreviated laparotomy was intra-abdominal injury in 21 patients (46.7%) and intra-abdominal sepsis in 24 patients (52.3%). There were no significant demographic differences between the two groups.

3.5.2 Primary Outcome:

3.5.2.1 Plasma PCT levels

Figure 2 summarizes plasma levels of PCT at baseline, 24 and 48 hours, and 1 week after TAC application. Plasma levels of PCT were significantly increased at 24 and 48 hours from baseline in patients randomized to ANPPT and BVP. At 1 week, the plasma PCT levels decreased close to baseline in the ANPPT but remained significantly higher in the BVP group compared to baseline (**Fig. 3**). However, the difference between the two groups was not significant at all time points (**Table 5**). When stratified by whether patients underwent abbreviated laparotomy for abdominal injury or intra-abdominal sepsis there remained to be no significant difference in plasma PCT levels between groups (**Table 6**).

3.5.2.2 Peritoneal PCT levels

Figure 4 summarizes peritoneal fluid procalcitonin level of PCT after abbreviated laparotomy. Although there was no significant difference in the volume of drained peritoneal fluid during the first 24 hours of therapy between the two groups (data not shown), the peritoneal levels of PCT were significantly lower in patients randomized to the ANPPT group versus BVP at 24 hours (p=0.004). The peritoneal PCT level continued to be lower in the ANPPT group at 48 hours as compared with that of BVP, with a notable trend to significance (p= 0.07) (**Table 7**).

3.5.3 Secondary Outcomes:

3.5.3.1 PCT and survival

Thirteen of the 45 patients died within 30 days after abbreviated laparotomy. The 30-day mortality was 13% for patients allocated to ANPPT and 45% for those fitted with the BVP

(p=0.02). The estimated OR for mortality was 0.15 (95% CI, 0.02 -1.04; P=0.05) after adjusting for baseline differences in age, gender, APACHE II score and SOFA score. Although plasma levels of PCT were higher among non-survivors than among survivors at 24 and 48 hours from baseline (**Fig. 5**), The difference between the two groups was not significant after adjusting for treatment group (P= 0.32 and 0.12, respectively). There was also no difference in the peritoneal levels of PCT between survivors and non-survivors at 24 hours (p= 0.59) and 48 hours (p= 0.26) after adjusting for treatment group.

3.6 Discussion

In the present study, although plasma levels of PCT were significantly increased up to 1 week from baseline in BVP, we found no statistically significant difference between patients randomized to the ANPPT versus BVP in the plasma PCT levels at 24, 48 hours, and 1 week. However, there was a significant difference in the intra-peritoneal levels of PCT between the two treatment groups at 24 and 48 hours. This significant difference is congruent with a hypothesis that active negative pressure peritoneal therapy with a more effective TAC device may modulate inflammation and induce a lower inflammatory response after abbreviated laparotomy as compared to a standard BVP.[4,79]

The Peritoneal VAC study observed a lower overall 30-day mortality rate for patients treated with the ANPPT. This overall reduced mortality is consistent with results from a multicenter prospective cohort study by Cheathman et al. where the 30-day mortality rate was 14% for patients treated with ABThera™ OA NPT versus 30% for those treated with BVP (p=0.01).[5] Similarly, in the Peritoneal VAC trial ANPPT was associated with a reduction in 90-day mortality when compared to BVP (22% versus 50% respectively, p=0.04).[8]

However, although there were lower PCT levels among survivors treated with ANPPT at 24 and 48 hours, improvement in survival was not explained by reduction in procalcitonin levels (both plasma and peritoneal fluid) after adjusting for treatment group. The exact mechanism resulting in improved survival in patients treated with ANPPT remains unclear. Experimental studies suggested active removal of cytokine-rich pro-inflammatory peritoneal fluid from the open abdomen mitigated the systematic inflammatory response and improved cardiac, pulmonary, gastrointestinal and renal function.[4,85] In addition, ANPPT might modulate intestinal microenvironment by mediating the innate immune system, which enables a more robust host defense.[86]

Microcirculation in the gut is disrupted in hemorrhagic and septic shock leading to tissue hypoxia, increased mucosal permeability, and release of pro-inflammatory mediators and ascites formation.[87-89] The damaged gut acts as reservoir rich in inflammatory mediators and provides a continual source of inflammation to the systemic circulation and is likely the initial motor of multiple organ dysfunction (MOD).[4,89-94] Basic science and animal studies have demonstrated that the concentrations of biomediators in the peritoneal fluid are many times higher than those in the systemic circulation,[95] and that peritoneal fluid is a profound activator of neutrophil priming.[96] Further laboratory work associates increased intra-peritoneal cytokines with adverse outcomes. Such associations in secondary peritonitis were investigated in a rat model of induced peritonitis. Measurement of intraperitoneal mediators at 24 and 72 hours found that intra-peritoneal cytokine levels (IL-6, TNF- α, and IL-10) significantly predicted survival.[95] The gross predictive value of such measurements also seems consistent at the bedside. A human study of 29 burn patients with severe intra-abdominal hypertension (IAH)/ abdominal compartment syndrome (ACS) measured cytokine levels in the peritoneum and in plasma and found that mortality was associated with

increased interferon-G, IL-10, Il-6, IL-4, and Il-2 in peritoneal fluid.[97] A study in 34 elective colorectal surgery patients compared cytokine levels in patients with anastomotic leakage (n=4) with those who had no leakage (n=30). In a seemingly simple fashion, peritoneal cytokine levels progressively decreased in those without anastomotic leakage and progressively increased in those with leakage, or peritonitis.[98]

Thus, there appears to be circumstantial evidence that intra-peritoneal cytokines are likely involved in the causation of poor outcomes in critical illness/injury, and even if not causal are at least markers of harmful processes. Mechanistically, there does also appear to be compartmentalization of these processes, meaning that local environments of mediators may be different from other compartments and their influence on the systemic outcomes dependent on tipping points such as transport factors[99,100]

Abbreviated laparotomy followed by TAC has been increasingly used among severely injured or critically ill patients in attempt to control ongoing hemorrhage or peritoneal soilage contributing to these physiological derangements prior to completing a definitive repair.[7,101,102] The concept of TAC in the management of open abdomen has evolved over the past two decades from passive drainage into vacuum assisted closure, which may be more efficient at removing pro-inflammatory peritoneal fluid and thus reducing concentration of inflammatory mediators in addition to promoting wound contraction and early fascial closure.[5,7] Although the precise mechanisms demand further study, current data have demonstrated the potential benefits of ANPPT as a TAC technique in the management of open abdomen. These promising findings need to be confirmed in larger multicenter trials.

3.7 Conclusion

Open abdomen management with ANPPT may modulate inflammation and induce a lower inflammatory response in the gut after abbreviated laparotomy. While open abdomen management with ANPPT associated with increased survival compared to BVP, manipulation of procalcitonin levels was not apparent, although differential manipulation of intra-peritoneal fluid and its inherent inflammatory potential should be studied further. Ultimately, the exact mechanism resulting in the improved survival still needs to be fully elucidated

Chapter Four: **Overall Discussion and Conclusions**

4.1 Key findings and discussion

Sepsis and organ dysfunction continue to be important complications after trauma and the main cause of late death in trauma. Early identification of patients at risk of developing posttraumatic complications is crucial to allow provision of early and appropriate therapy and hence improve clinical outcomes and mortality. Although we were not able to perform a met-analysis, our review showed that plasma levels of procalcitonin may play a role as a surrogate biomarker in trauma. PCT levels can be used to differentiate systemic inflammation from sepsis. PCT is easy to measure, sensitive, specific and very reliable. Its kinetics correlate with severity of injury, development of sepsis and MOD and predicted mortality in trauma population, which may help to identify those at risk of posttraumatic complications.

Although use of open abdomen in trauma and severe intra-peritoneal sepsis is controversial, recent studies have demonstrated that TAC with ANPPT have been associated with improved outcomes and survival. In our study we performed a retrospective analysis of the Intraperitoneal Vacuum Trial. The trial demonstrated that management with ANPPT through ABThera was associated with improved survival compared to Barker's Vacuum Pack (BVP), which is a more passive TAC technique. We specifically examined the behavior and associations of plasma procalcitonin levels in patients randomized to ANPPT versus BVP. In addition, we explored association of peritoneal levels of PCT and clinical outcomes. We observed patients in both treatment groups had peak plasma PCT levels at 24 hours. Plasma levels of PCT decreased thereafter in the ANPPT group to close to baseline at 1 week, while it remained significantly higher in the BVP group at 1 week. Although there was no difference in the levels of plasma PCT between

the two treatment groups at all time points, the kinetics of plasma PCT was similar to that reported in previous studies.

Interestingly, patients who were treated with ANPPT had significantly lower peritoneal levels of PCT at 24 and 48 hours. This is in accordance with our hypothesis that ANPPT device may modulate inflammation in the gut resulting in a lower inflammatory response after abbreviated laparotomy as compared to a standard BVP. We did not observe significant difference in the plasma PCT levels. This large gradient in PCT levels between the peritoneal cavity and plasma highlights the importance of compartmentalization of innate immune response.

Experimental studies suggested active removal of cytokine-rich pro-inflammatory peritoneal fluid from the open abdomen through ANPPT mitigated the systematic inflammatory response and improved cardiac, pulmonary, gastrointestinal and renal function. In our study we observed improved survival in patient treated with ANPPT as compared to BVP. We observed higher plasma PCT levels in non-survivors. Most importantly, declining levels of PCT were observed in the survivors group after 24 hours. However, our results were not statistically significant and hence were not able to explain improvement in survival by reduction in the PCT levels alone. The mechanism resulting in improved survival in patients required OA management with ANPPT still needs be fully elucidated.

4.2 Future research directions

Further studies are necessary to explain the mechanism by which ANPPT in the OA management reduces inflammation and increases survival rate. Studies should also focus on the peritoneal levels of cytokines as local mediators and their influence on the systemic outcomes may be different from other compartments.

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Table 1: Details of study characteristics of included studies in the systematic review

Study	Study design	Study setting	No. of patients	Mortality %	Peak PCT level	PCT level predicting outcomes		
						Sepsis	MODS	Death
Ren et al.[42] (China, 2016)	Prospective Case Control	Trauma surgical department	56	-	Day1&2	Yes	-	-
Wojtaszek et al.[43] (Poland, 2014)	Prospective Cohort	-	45	Data not shown	Day 1	No	-	Yes
Rajkumari et al.[44] (India, 2013)	Prospective Case Control	SICU	275	10	-	Yes	No	-
Sakran et al.[45] (USA, 2012)	Prospective Cohort	Trauma ICU	102	13	Day 1&2	Yes	-	Yes
Haasper et al.[46] (Germany, 2010)	Prospective Cohort	ICU	94	12	Day 2&3	No	Yes	-

Keel et al.[47] (Switzerland, 2009)	Prospective Cohort	Trauma center	83	12	Day 1	Yes	-	-
Castelli et al.[48] (Italy, 2009)	Prospective Cohort	ICU	94	5	Day 1	Yes	Yes	-
Billeter et al.[49] (Switzerland, 2009)	Retrospective cohort	SICU	1032	10	Day 1	Yes	-	-
Maier et al.[50] (Germany, 2009)	Prospective Cohort	-	74	-	Day 1	-	-	-
Balci et al.[51] (Turkey, 2009)	Prospective Cohort	SICU	113	44	Day 1 & 7	Yes	-	Yes
Castelli et al.[52] (Italy, 2006)	Prospective Cohort	ICU	49	-	Day 1	Yes	Yes	-

Ertugrul et al.[53] (Turkey, 2006)	Prospective Case Control	SICU	41	-	-	No	-	-
Meisner et al.[54] (Germany, 2006)	Prospective Cohort	ICU	90	17	Day 1	Yes	No	Yes
Egger et al.[55] (Austria, 2004)	Prospective Cohort	ICU	26	-	-	Yes	-	-
Hensler et al.[56] (Germany, 2003)	Prospective Case Control	Trauma center	137	11	Day 1+2 combined	No	Yes	No
Andermahr et al.[57] (Germany, 2002)	Prospective Case Control	ICU	133	21	Day 1	No	-	-
Oberholzer et al.[58] (Switzerland, 2000)	Prospective Case Control	Trauma center	1276	7	Day 1	Yes	Yes	-

Wanner et al.[59] (Germany, 2000)	Retrospective Case Control	ICU	405	23	Day 1 &3	Yes	Yes	No
Mimoz et al.[60] (France, 1998)	Prospective Cohort	SICU	21	14	Day 1	No	Yes	-

Abbreviations: ICU= Intensive care unit, SICU= Surgical intensive care unit, PCT=procalcitonin, MODS= Multiple organ dysfunction syndrome

Table 2: Assessment of risk of bias using QUIPS tool

Study	**Participation**	**Attrition**	**Prognostic factor measurement**	**Outcome measurement**	**Study confounding**	**Statistical analysis**
Ren et al.[43]	High	High	Moderate	High	Moderate	Moderate
Wojtaszek et al.[43]	High	Moderate	Low	Moderate	Moderate	High
Rajkumari et al.[44]	Moderate	Low	High	Low	High	Moderate
Sakran et al.[45]	Low	Low	Low	Low	Low	Low
Haasper et al.[46]	Low	Low	Low	Low	Moderate	Moderate

Keel et al.[47]	Low	Low	Low	Moderate	Moderate	Low
Castelli et al.[48]	Moderate	Low	Low	Low	Low	Moderate
Billeter et al.[49]	Moderate	Low	Low	Low	Low	Low
Maier et al.[50]	Low	Moderate	Low	Low	Moderate	High
Balci et al.[51]	Low	Moderate	Low	Moderate	Moderate	High
Castelli et al.[52]	Low	Low	Low	Low	High	Low
Ertugrul et al.[53]	Moderate	Moderate	Moderate	Low	High	Moderate

Meisner et al.[54]	Low	Low	Low	Moderate	Low	Low
Egger et al.[55]	High	Moderate	Moderate	Low	High	Moderate
Hensler et al.[56]	Low	Low	Low	Low	Low	Low
Andermahr et al.[57]	Low	Moderate	Moderate	Low	Low	Low
Oberholzer et al.[58]	Low	Low	Low	Moderate	Low	Low
Wanner et al.[59]	Low	Moderate	Low	Low	Low	Low
Mimoz et al.[60]	Low	Low	Low	Low	Moderate	Moderate

Table 3. Prognostic values of other biomarkers studied simultaneously with serum PCT levels

Study	Other biomarkers	Comments on other biomarkers
Ren et al.[42]	HSP70, WBC	- HSP70 and WBC levels were elevated at 1-6 hours post injury while PCT increased 24 hours post - Magnitude of HSP70 increased was related to the severity of injury - Increased HSP70 24 hours post injury suggested infection
Rajkumari et al.[44]	CRP	- No difference in CRP levels between patients with and without sepsis - PCT and CRP did not correlate with SOFA score
Haasper et al.[46]	IL-6	- IL-6 levels peaked on day 0, while PCT peaked levels peaked on day 1 - Significant difference in IL-6 and PCT levels between patients with and without MODS - No difference in IL-6 and PCT levels between patients with and without sepsis
Keel et al.[47]	PSP, CRP, IL-6	- Significant difference in PSP levels between patients with and without sepsis during hospital stay - Slow induction of CRP with peak levels reaching day 3. Significant difference in CRP levels between patients with and without sepsis on day 7 after trauma.

		- Peak IL-6 levels of day 0 after trauma. Significantly higher IL-6 levels in septic patients after day 5 compared to patients with no infection - Peak PCT on day 1. Significant PCT levels between patients with sepsis and without on day 1,3,5,7 and 14 - No difference in CRP, PCT and IL-6 levels between patients with sepsis and local infection.
Castelli et al. [48]	CRP	- No difference in CRP levels between patients with and without sepsis - CRP did not correlate with SOFA score
Billeter et al.[49]	CRP, IL-6, lactate	-IL-6 peaked on day 1 after trauma - Significant difference in IL-6 levels between patients with or without sepsis on day 3 and 5. No difference after day 5 - Slow induction of CRP with peak levels reaching between day 3 and 7 - Significant difference in CRP levels between patients with or without sepsis on day 5,7 and 14 - Insufficient 24-hour lactate clearance was associated with high rate of mortality and sepsis
Balci et al.[51]	CRP	- CRP levels were higher only in cases of severe sepsis or septic shock, but not in cases of sepsis alone - Significant difference in CRP level between survivors and non-survivors on day 1 and 7

Castelli et al.[52]	CRP	- Slow induction of CRP after trauma - No correlation between CRP levels and sepsis - CRP levels correlated with SOFA score
Ertugrul et al.[53]	CRP	- No Difference in CRP levels between infected and non-infected groups
Meisner et al.[54]	CRP	- CRP levels peaked on Day 3 (slow induction) - No correlation between CRP levels and posttraumatic complications including sepsis, MODS and mortality
Egger et al.[55]	PMN migratoin, CRP,IL-6, IL-8, NT, lactate, cortisol, Elastase, MDA	- PMN migration was a highly sensitive predictive marker for infection - No difference in the other biomarkers levels between infected and non-infected group
Hensler et al.[56]	Neopetrin (NT)	- NT level decreased on day 0 after trauma, followed by an increase on days 1 and 2 - Both PCT and NT were unable to differentiate between patients who developed sepsis or not - No difference between PCT or NT levels of survivors and non-survivors - No difference in NT levels between patients with and without MOF

Oberholzer et al.[58]	IL-6	Both PCT and IL-6 levels peaked on day 1 after trauma Both PCT and IL-6 levels were significantly higher in septic patients compared with patients without sepsis Both PCT and IL-6 levels were significantly higher in patients who developed MODS compared with patients without MODS
Mimoz et al.[60]	CRP	- PCT levels peaked on day 1 while CRP levels peaked on day 2 after trauma - Both Peak PCT and CRP levels were higher in patients who subsequently developed MODS

Abbreviations: HAI= Hospital acquired infection. CRP=C-reactive protein, IL=Interleukin, PCT=procalcitonin, NT= Neopetrin, PMN= polymorphonuclear leucocyte, PSP= Pancreatic stone protein. SOFA= sequential organ failure assessment, MODS= Multiple organ dysfunction syndrome. MDA=malondialdehyde

Table 4. Baseline characteristics of patients enrolled in the Intraperitoneal Vacuum Trial

Parameter	**ABThera™ (n=23)**	**Barker's vacuum pack (n=22)**	**P value**
Age in years, median (IQR)	56 (39-71)	56 (33-68)	0.83
Gender, Male n (%)	19 (82.6)	18 (81.1)	0.95
Etiology Intra-abdominal injury n (%)	10 (43.5)	11 (50.0)	0.77
GCS, median (IQR)	14 (9-15)	12 (3-14)	0.14
ISS for trauma patients only, mean ± SD	26.4 ± 10.9	30.3 ± 10.0	0.41
APACHE II score, mean ± SD	22.2 ± 9.0	26.6 ± 11.9	0.17
Charlson morbidity score, median (IQR)	3 [1-5]	2 [0-3]	0.06
SOFA score	7.7± 3.9	9.4 ± 4.7	0.19

Abbreviations: GCS= Glasgow Coma Scale, ISS= Injury Severity Score, APACHE= Acute Physiology and Chronic Health Evaluation, SOFA= Sequential Organ Failure Assessment, SD=standard deviation, IQR=Interquartile range

Table 5. Plasma level of procalcitonin between baseline and 24 hours, 48 hours and 1 week by treatment group

Treatment Group	**Baseline (ng/mL)**	**24 hours (ng/mL)**	**p-value for difference at 24h between groups**	**48 hours (ng/mL)**	**p-value for difference at 48h between groups**	**1 week (ng/mL)**	**p-value for difference at 1 week between groups**
ABThera™	8.7 [7.1-9.3]	10.0 [8.4-11.9]	0.40	9.5 [8.7-12.2]	0.54	8.8 [7.9-9.9]	0.23
Barker's vacuum pack	9.0 [7.5-16.2]	11.2 [8.8-20.8]		10.8 [8.8-16.9]		9.8 [9.0-11.6]	

Table 6. Plasma level of PCT at baseline, and 24 and 48 hours after TAC application among patients with abdominal injury intra-abdominal sepsis

Etiology of abbreviated laparotomy	Treatment group	Baseline (ng/ml)	24h (ng/ml)	P-value for difference at 24h between groups	48h (ng/ml)	P-value for difference at 48h between groups	1 week (ng/mL)	P-value for difference at 48h between groups
Abdominal injury	ABThera	7.3 (6.6-8.6)	9.9 (8.3-17.8)	0.27	9.4 (8.7-13.4)	0.25	8.9 (8.1-11.0)	0.89
	Barker's Vacuum Pack	7.5 (5.8-8.0)	8.7 (8.2-9.7)		8.5(8.0-9.2)		8.9 (8.4-9.1)	
Intra-abdominal sepsis	ABThera	9.3 (8.7-9.9)	10.1 (9.0-11.0)	0.81	9.8 (8.6-12.2)	0.56	8.8 (6.9-9.0)	0.81
	Barker's Vacuum Pack	16.2 (9.6-21.9)	20.5 (11.2-26.1)		16.6 (12.0-18.7)		11.4 (9.8-14.5)	

Table 7. Peritoneal level of procalcitonin between 24 and 48 hours versus baseline by treatment group

Treatment Group	**Baseline (ng/mL)**	**24 hours (ng/mL)**	**p-value for difference at 24h between groups**	**48 hours (ng/mL)**	**p-value for difference at 48h between groups**
ABThera™	4.3 [2.6-5.3]	3.1 [2.5-4.9]	0.004	4.2 [2.4-7.0]	0.07
Barker's vacuum pack	4.6 [3.7-6.1]	5.5 [3.2-16.2]		5.9 [4.2-11.1]	

Figure 1: Flow diagram of selected studies for review

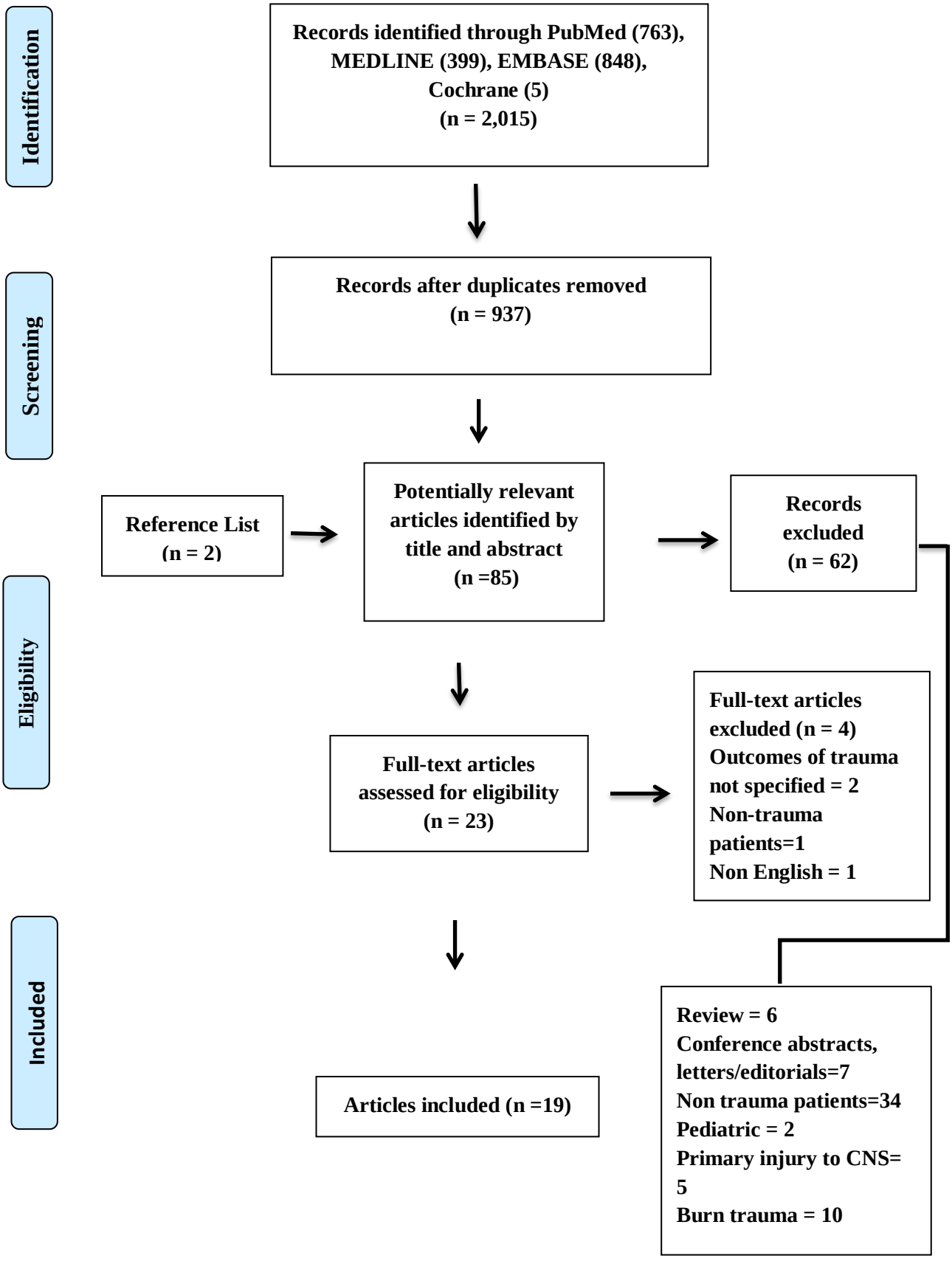


Figure 2. Plasma Procalcitonin Levels After Abbreviated Laparotomy

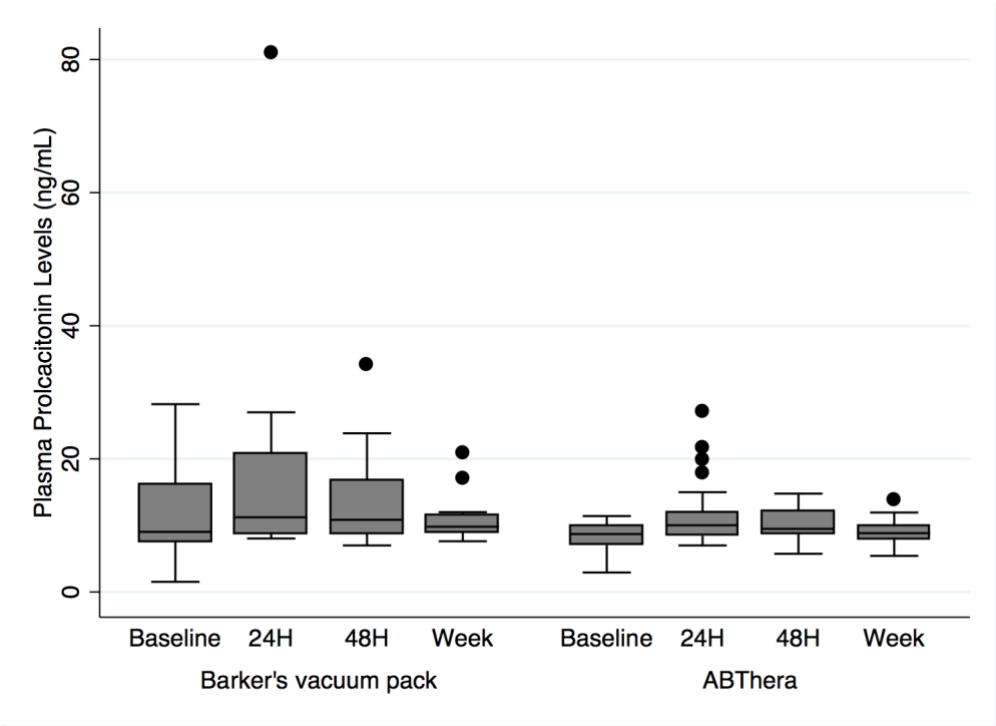


Figure 3: Mean (95% CI) Changes from Baseline Plasma Procalcitonin at 24hr, 48hr and Week 1 After Abbreviated Laparotomy

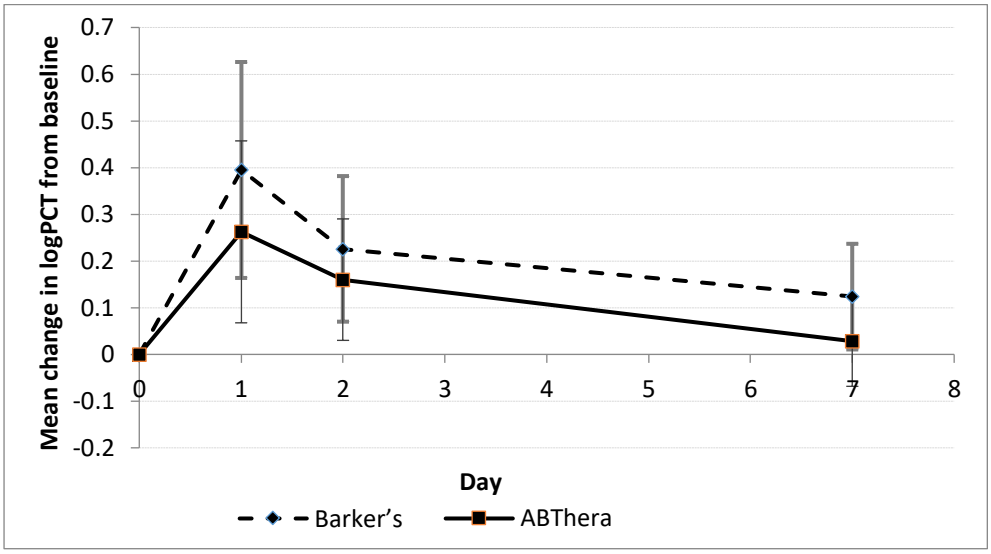


Figure 4. Peritoneal Procalcitonin Levels After Abbreviated Laparotomy

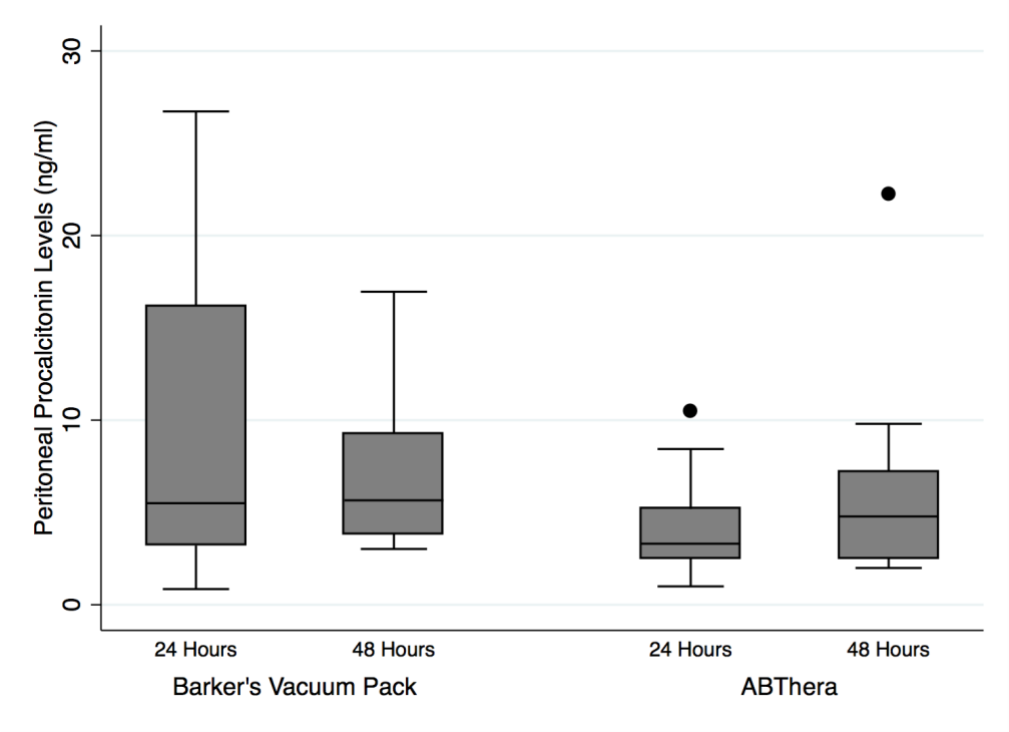
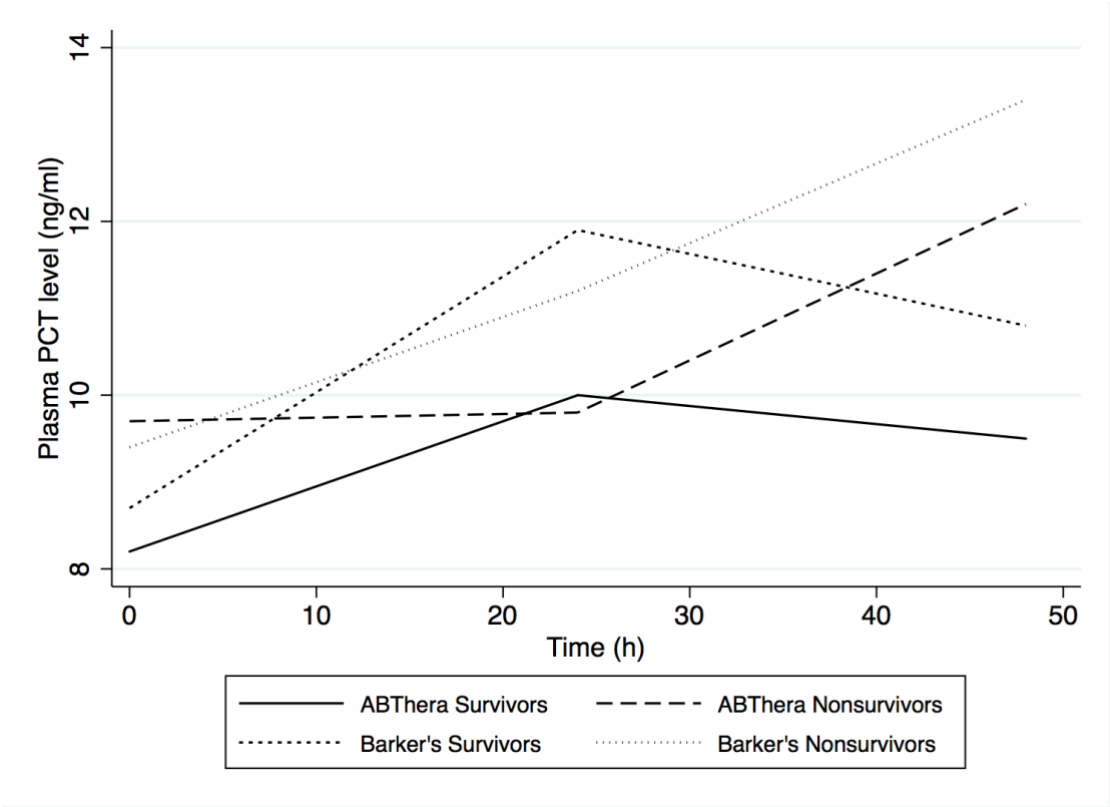


Figure 5. Median Plasma Levels Among Survivors and Non-survivors by Treatment Group



Search Strategy

PubMed

(("procalcitonin"[Supplementary Concept] OR "procalcitonin"[All Fields]) OR PCT[All Fields]) AND (("injuries"[Subheading] OR "injuries"[All Fields] OR "trauma"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields]) OR ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "injury"[All Fields]) OR ("injuries"[Subheading] OR "injuries"[All Fields] OR "wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields]) OR ("wounds and injuries"[MeSH Terms] OR ("wounds"[All Fields] AND "injuries"[All Fields]) OR "wounds and injuries"[All Fields] OR "wound"[All Fields]))

N=763

Medline

1. exp "Wounds and Injuries"/

2. (trauma or injur* or wound*).kw,tw.

3. 1 or 2

4. procalcitonin.mp.

5. 3 and 4

N= 399

EMBASE

1. injury/ or abdominal injury/ or blunt trauma/ or crush trauma/ or multiple trauma/ or pelvis injury/ or seatbelt injury/ or wound/

2. (trauma or injur* or wound*).kw,tw.

3. 1 or 2

4. exp procalcitonin/

5. 3 and 4

N=848

Appendix 2: Data abstraction form for systematic review

Author	Year and place of publication	Study design	Study setting	Study size	ISS	PCT assay	PTC kinetics	Other biomarkers	Reported outcomes			
									Injury severity	Sepsis	MOD	Mortality

Abbreviations: PCT=procalcitonin, ISS= Injury Severity Score, MOD= Multiple organ dysfunction