DOI：10.6314/JIMT.202508_36(4).04 內科學誌 2025：36：264-271

Procalcitonin in Heatstroke and Rhabdomyolysis: Diagnostic Pitfalls and Prognostic Promise

Chin-Ho Kuo, MD[1], Hsin-An Lin, MD, PhD[2], Chien-Chou Chen, MD[3,4]

[1]Division of Cardiology, Department of Medicine,
Tri-Service General Hospital Songshan branch,
National Defense Medical University, Taipei, Taiwan, R.O.C.
[2]Division of Infection, Department of Medicine,
Tri-Service General Hospital Songshan branch,
National Defense Medical University, Taipei, Taiwan, R.O.C.
[3]Division of Nephrology, Department of Medicine,
Tri-Service General Hospital Songshan branch,
National Defense Medical University, Taipei, Taiwan, R.O.C.
[4]Department of Medicine, National Defense Medical University,
Taipei, Taiwan, R.O.C.

Abstract

Heatstroke is a life-threatening emergency characterized by elevated core body temperature and systemic inflammatory response, often resulting in multiorgan dysfunction. Exertional heatstroke (EHS), typically affecting young and active individuals, is frequently complicated by rhabdomyolysis (RM), a condition marked by skeletal muscle breakdown and the release of intracellular contents into the circulation. This process can provoke a sterile inflammatory response that closely mimics bacterial sepsis, posing significant diagnostic challenges. Serum procalcitonin (PCT), a widely recognized biomarker for bacterial infection and sepsis, has also been shown to rise in non-infectious conditions such as trauma, burns, and heat-related illness. In the context of EHS-associated RM, elevated PCT is more likely to reflect the severity of systemic inflammation and tissue injury rather than the presence of a true infection. Misinterpretation of PCT in this setting may lead to inappropriate antimicrobial use and suboptimal patient management. This review synthesizes current evidence on the relationship between RM and PCT in heat injury, emphasizing the pathophysiological mechanisms of PCT elevation, its limitations in infection discrimination, and its potential role as a prognostic biomarker. Clinicians are encouraged to interpret PCT levels in conjunction with clinical findings, temporal trends, and adjunctive markers to improve diagnostic precision and guide appropriate therapeutic strategies.

Key Words: Heatstroke; Rhabdomyolysis; Procalcitonin

Reprint requests and correspondence：Dr. Chien-Chou Chen, MD
Address：Division of Nephrology, Department of Medicine, Tri-Service General Hospital Songshan branch, National Defense Medical Center, Taipei, Taiwan, R.O.C.

Introduction

Exertional heatstroke (EHS) is a medical emergency characterized by sustained hyperthermia and systemic inflammatory response, frequently leading to multiorgan dysfunction[1]. It predominantly affects healthy young individuals such as athletes and military personnel exposed to intense physical exertion in hot and humid environments[2-4]. A common and severe complication of EHS is rhabdomyolysis (RM), a syndrome resulting from the breakdown of skeletal muscle fibers and subsequent release of intracellular components, including myoglobin, creatine kinase (CK), electrolytes, and sarcoplasmic enzymes,into the circulation[5-7]. RM may manifest clinically with myalgia, muscle swelling, weakness, and dark-colored urine, often without hematuria. Etiologically, RM is classified into traumatic, exertional, and non-exertional types; among these, exertional RM is most closely associated with EHS[8].

The systemic inflammatory response triggered by RM can closely resemble that of bacterial sepsis, complicating clinical interpretation and management, particularly in acute care settings[9]. Procalcitonin (PCT), a 116-amino acid peptide primarily produced by thyroid C-cells, is widely used as a biomarker for bacterial infections and sepsis[10]. However, in the context of non-infectious inflammation such as EHS and RM, PCT can be significantly elevated due to extrathyroidal synthesis—particularly in the liver, lungs, and muscle—stimulated by proinflammatory cytokines including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). Additional mechanisms such as muscle-derived calcitonin gene-related peptide (CGRP) expression may further augment PCT production[11,12].

Importantly, the interpretation of PCT in the EHS-RM population is particularly problematic when compared to other inflammatory syndromes such as trauma or pancreatitis. Unlike trauma or surgery, where a clear temporal link exists between insult and biomarker rise, EHS often involves a delayed and variable presentation, further obscured by physical exertion and environmental stress[13]. Additionally, the coexistence of massive muscle injury, gut barrier dysfunction, and intense cytokine surge in EHS uniquely amplifies PCT production in a manner that closely mimics bacterial sepsis, even in the absence of infection. This convergence of sterile inflammatory pathways renders PCT a less specific marker in this context, heightening the risk of diagnostic error and overtreatment with antimicrobials.

Recent studies, including a 10-year ICU cohort study by Zhong et al., demonstrate that serum PCT levels in EHS patients correlate strongly with serum myoglobin, Sequential Organ Failure Assessment (SOFA) or Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, supporting its association with organ dysfunction severity rather than bacterial infection per se[6]. Consequently, elevated PCT in EHS-associated RM may reflect the magnitude of sterile inflammation and tissue injury rather than true infection. This poses a diagnostic challenge, as misinterpretation of elevated PCT may lead to unnecessary antimicrobial use, increased healthcare costs, and suboptimal clinical management.

This review aims to provide an updated synthesis of the relationship between PCT and RM in the context of heat injury, emphasizing the underlying pathophysiological mechanisms, diagnostic limitations, prognostic significance, and implications for evidence-based clinical decision-making.

Pathophysiological Mechanisms of PCT Elevation in Heatstroke

The elevation of serum PCT in EHS, particularly when complicated by RM, reflects a convergence of sterile inflammatory pathways rather than microbial invasion. The primary driver is widespread skeletal muscle breakdown, which releases

intracellular contents, such as myoglobin, creatine kinase, potassium, and phosphate—into the circulation. These molecules function as damage-associated molecular patterns (DAMPs), which activate pattern recognition receptors (e.g., Toll-like receptors) on innate immune cells and initiate downstream cytokine cascades[9].

Key inflammatory mediators, including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β), are upregulated in response to DAMPs and play a central role in stimulating extrathyroidal PCT synthesis, particularly in the liver, lung, and adipose tissues[9,11,14]. This cytokine-driven mechanism mimics the host response to bacterial infection, complicating the interpretation of elevated PCT levels in heat-related illness. Additionally, gastrointestinal barrier dysfunction has been identified as a unique feature of EHS. Heat-induced intestinal ischemia and hyperpermeability may permit the translocation of lipopolysaccharides (LPS) into the systemic circulation, further amplifying the inflammatory response[15]. Evidence from military cohort studies demonstrated that patients with antecedent gastrointestinal symptoms exhibited significantly higher PCT levels, reinforcing the hypothesis that gut-derived endotoxemia exacerbates cytokine-mediated PCT induction[6] (Figure 1).

Unlike trauma or surgical stress, where the onset of injury is temporally well-defined, EHS often presents with delayed and variable biomarker kinetics due to prolonged exertion and environmental factors[13]. Thus, the combination of massive tissue injury, cytokine storm, and possible endotoxemia renders PCT elevation in EHS a non-specific but potent signal of systemic inflammatory stress, limiting its utility as a sole marker for infection. This pathophysiological complexity necessitates cautious clinical interpretation of PCT in the management of EHS and RM.

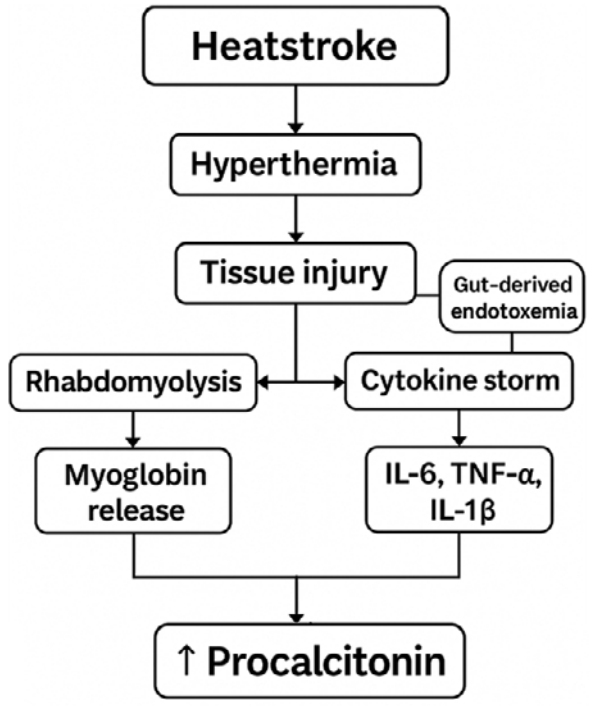

Figure 1.

Correlation Between PCT and Rhabdomyolysis in EHS

Emerging evidence supports a robust association between elevated PCT levels and the development of RM in the setting of EHS. In a large ICU-based cohort study by Zhong et al., which included 162 patients with EHS, PCT levels were significantly higher in patients with RM compared to those without. These elevations correlated with serum myoglobin, creatine kinase, and organ dysfunction indices such as SOFA and APACHE II scores[6]. The authors further applied a two-piecewise linear regression model, revealing a nonlinear association with a threshold at 4.6 ng/mL, below which PCT levels were predictive of RM, but above which their diagnostic yield plateaued. This nonlinear pattern suggests saturation of inflammatory signaling or biomarker kinetics at higher levels of systemic injury (Table 1).

Table 1. Summary of Clinical Studies Assessing Diagnostic and Prognostic Value of Serum Procalcitonin in Heatstroke and Rhabdomyolysis

Study	Population & setting	Main Findings	Implication on PCT
Tong et al., 2012[17]	68 EHS patients (ICU), China	PCT correlated with MODS, mortality, and rhabdomyolysis severity	Independent predictor of mortality, not infection-specific
Zhong et al., 2024[6]	162 EHS patients (ICU), China	PCT correlated with myoglobin, DIC, AHI, SOFA, APACHE II	Nonlinear association with RM; predictive of organ dysfunction
Hausfater et al., 2008[22]	53 classic heatstroke patients, France	PCT elevated even in absence of bacterial infection	Indicator of severity, not useful for infection diagnosis
Wang et al., 2023[16]	225 classic heatstroke patients, China	Developed prognostic nomogram incorporating PCT, significantly predicting 7-day survival. PCT ≥1 ng/ml independently associated with increased mortality.	Supports using PCT in composite prognostic scores.

Abbreviations: EHS, exertional heatstroke; RM, rhabdomyolysis; PCT, procalcitonin; MODS, multiple organ dysfunction syndrome; DIC, disseminated intravascular coagulation; AHI, acute hepatic injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; SOFA, Sequential Organ Failure Assessment; CHS, classic heatstroke; ICU, intensive care unit.

These findings align with observations from classic heatstroke studies, including early work by Nylen et al., which demonstrated elevated PCT in the absence of infection, likely reflecting cytokine-mediated responses to tissue injury rather than microbial stimulation[11]. Collectively, these studies suggest that PCT behaves as an acute-phase reactant in EHS-RM, influenced by DAMPs and systemic cytokine release. While not specific for RM, PCT may serve as a biomarker of inflammatory burden and tissue disruption, warranting further investigation into its role in risk stratification.

In addition to its value as a single biomarker, recent evidence supports incorporating PCT into composite prognostic models to enhance risk stratification in heat-related illness. In a multicenter cohort study of classic heatstroke, Wang et al. developed and validated a prognostic nomogram combining PCT with clinical variables including heart rate, Glasgow Coma Scale (GCS), body temperature, aspartate aminotransferase (AST), and diarrhea[16]. This model exhibited excellent predictive accuracy (AUC: 0.994 training cohort; 0.901 validation cohort) and reliably differentiated high-risk from low-risk patients based on 7-day survival. Notably, a PCT level ≥1 ng/ml independently predicted increased in-hospital mortality. These findings further confirm the utility of PCT as a valuable prognostic marker within multidimensional risk models, enabling more precise clinical management in heatstroke patients.

Diagnostic Limitations and Implications for Antibiotic Stewardship

PCT is widely recognized as a valuable biomarker for the early detection of bacterial sepsis; however, its diagnostic specificity is notably reduced in non-infectious inflammatory conditions, such as EHS complicated by RM[17,18]. In these clinical scenarios, elevated PCT levels predominantly reflect the extent of sterile systemic inflammation and tissue injury rather than a genuine infectious process. A critical clinical concern arises from the potential for delayed or inappropriate therapeutic

interventions if clinicians rely exclusively on PCT values to guide antibiotic decision-making. Indeed, isolated interpretation of elevated PCT without corroborating clinical, microbiological, or laboratory evidence could inadvertently delay essential antimicrobial therapy in patients with actual infections.

Consequently, we strongly emphasize that PCT results must not be interpreted in isolation. Instead, clinical decision-making should integrate PCT data with thorough clinical assessments, microbiological findings, and additional laboratory parameters, including C-reactive protein (CRP), white blood cell (WBC) counts, and lactate levels. Such an integrated approach is essential to optimize diagnostic accuracy, ensure timely intervention, and avoid treatment delays.

The limited specificity of PCT in these contexts has substantial implications for antimicrobial stewardship. Excessive reliance on PCT as a binary decision-making tool for antibiotic initiation or continuation risks unnecessary antimicrobial exposure, leading to overtreatment in patients without genuine infections. Such inappropriate antibiotic use not only increases healthcare costs and lengthens hospital stays but also exacerbates the global public health threat of antimicrobial resistance (AMR)[19]. This issue is especially pertinent in intensive care settings, where patients with EHS often empirically receive broad-spectrum antibiotics due to presumptive risk of sepsis.

Given these challenges, the clinical interpretation of PCT must occur within a broader diagnostic framework. Factors such as timing and trends of PCT measurement, clinical presentation, microbiological cultures, and presence or absence of localizing infection signs must all be considered. Furthermore, integrating validated scoring systems such as SOFA or APACHE II scores, along with additional biomarkers like CRP and lactate, can substantially enhance diagnostic precision.

Prognostic Role of PCT in Heatstroke

Beyond its diagnostic role, increasing evidence underscored the prognostic utility of PCT compared to traditional biomarkers such as CRP and CK in critically ill patients, including those suffering from heat-related illness[6,20,21]. Clec'h et al. demonstrated that PCT was superior to CRP in predicting mortality among critically ill ICU patients with systemic inflammation, underscoring its robustness as a prognostic indicator [20]. Likewise, Charles et al. found that serial PCT measurements were independent predictors of mortality in patients with septic shock, further supporting the biomarker's prognostic relevance in critical illness[21].

In the specific context of EHS, a 10-year retrospective cohort study by Zhong et al. showed that admission PCT levels were significantly higher in non-survivors than in survivors. Receiver operating characteristic (ROC) analysis yielded a moderate predictive value for 90-day mortality (AUC 0.705), although this was inferior to the prognostic accuracy of the APACHE II scoring system (AUC 0.857)[6]. Nevertheless, the rapid availability and ease of PCT testing supports its practical value for early risk stratification and prompt identification of patients at increased risk of adverse outcomes in acute care settings

Crucially, the prognostic value of PCT in heatstroke patients is not contingent upon its specificity for infectious processes. Rather, elevated PCT levels reflect the intensity of systemic inflammation and severity of tissue injury, key pathophysiological factors influencing mortality in heatstroke. In clinical settings where advanced prognostic scoring may not be immediately available, initial or serial PCT measurements could provide timely signals of clinical deterioration, potentially guiding early intervention decisions.

Recommendations for Clinical Use

Given the nonspecific nature of PCT elevation in EHS and RM, clinicians must adopt a nuanced and context-driven approach to its interpretation. Rather than relying on single, absolute PCT values, clinical decision-making should integrate PCT trends with other laboratories and clinical indicators. Adjunctive markers such as CRP, WBC count, lactate, and CK can provide complementary information regarding the inflammatory burden, tissue injury, and perfusion status. Concurrent use of validated severity scoring systems—such as the APACHE II and SOFA, can further enhance prognostic accuracy.

Serial measurement of PCT over time is particularly useful in distinguishing persistent inflammation from resolving processes. A sustained or rising PCT trajectory in the absence of confirmed infection may indicate continued tissue injury or inflammatory activation, whereas a declining trend may reflect recovery and can help guide de-escalation of supportive interventions. Moreover, clinicians should exercise caution in initiating or continuing antimicrobial therapy based solely on elevated PCT levels, especially in the absence of microbiologic evidence. Ultimately, PCT should be viewed not as a binary marker of infection but as one component of a comprehensive, individualized diagnostic algorithm tailored to the complex pathophysiology of heat-related illness.

Future Directions

Although PCT lacks specificity in differentiating infection from sterile inflammation, it remains a promising adjunctive biomarker for evaluating illness severity and inflammatory burden in heat-related syndromes. Its rapid turnaround time and widespread clinical availability render it particularly valuable in time-sensitive environments such as emergency departments and intensive care units. Moving forward, research efforts should prioritize the establishment of validated, heatstroke-specific PCT thresholds that can better stratify patient risk and guide management decisions. In parallel, longitudinal studies are needed to evaluate the prognostic value of serial PCT kinetics in tracking disease progression and therapeutic response. Additionally, the integration of PCT into composite clinical algorithms, alongside scoring systems such as SOFA or APACHE II, may enhance triage accuracy and resource allocation in critical care. Importantly, such algorithms should be tested prospectively across diverse patient populations, including those with exertional and classic heatstroke, to ensure generalizability. As our understanding of heat-related pathophysiology evolves, the role of PCT should be refined to support precision medicine approaches in acute care settings.

References

1. Bouchama A, Knochel JP. Heat stroke. N Engl J Med 2002;346(25):1978-88.
2. Misset B, De Jonghe B, Bastuji-Garin S, et al. Mortality of patients with heatstroke admitted to intensive care units during the 2003 heat wave in France: a national multiple-center risk-factor study. Crit Care Med 2006;34(4):1087-92.
3. Semenza JC, Rubin CH, Falter KH, et al. Heat-related deaths during the July 1995 heat wave in Chicago. N Engl J Med 1996;335(2):84-90.
4. Dhainaut JF, Claessens YE, Ginsburg C, Riou B. Unprecedented heat-related deaths during the 2003 heat wave in Paris: consequences on emergency departments. Crit Care 2004;8(1):1-2.
5. Bouchama A, Abuyassin B, Lehe C, et al. Classic and exertional heatstroke. Nat Rev Dis Primers 2022;8(1):8.
6. Zhong L, Shuai F, Wang C, Han L, Liu Z, Wu M. Serum procalcitonin levels are associated with rhabdomyolysis following exertional heatstroke: an over 10-year intensive care survey. World J Emerg Med 2024;15(1):23-7.
7. Luan Y, Huang E, Huang J, et al. Serum myoglobin modulates kidney injury via inducing ferroptosis after exertional heatstroke. J Transl Int Med 2023;11(2):178-88.
8. Yang BF, Li D, Liu CL, et al. Advances in rhabdomyolysis: A review of pathogenesis, diagnosis, and treatment. Chin J Traumatol 2025;S1008-1275(25)00010-0.
9. Lu KC, Wang JY, Lin SH, Chu P, Lin YF. Role of circulating cytokines and chemokines in exertional heatstroke. Crit Care Med 2004;32(2):399-403.
10. Lin KH, Wang FL, Wu MS, et al. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection in patients with liver cirrhosis: a systematic review and meta-

analysis. Diagn Microbiol Infect Dis 2014;80(1):72-8.
11. Nylén ES, Al Arifi A, Becker KL, Snider RH, Jr., Alzeer A. Effect of classic heatstroke on serum procalcitonin. Crit Care Med 1997;25(8):1362-5.
12. Bouchama A, Parhar RS, el-Yazigi A, Sheth K, al-Sedairy S. Endotoxemia and release of tumor necrosis factor and interleukin 1 alpha in acute heatstroke. J Appl Physiol (1985) 1991;70(6):2640-4.
13. Wu M, Wang C, Liu Z, Liu Z. Sequential Organ Failure Assessment Score for Prediction of Mortality of Patients With Rhabdomyolysis Following Exertional Heatstroke: A Longitudinal Cohort Study in Southern China. Front Med (Lausanne) 2021;8:724319.
14. Hall DM, Buettner GR, Oberley LW, Xu L, Matthes RD, Gisolfi CV. Mechanisms of circulatory and intestinal barrier dysfunction during whole body hyperthermia. Am J Physiol Heart Circ Physiol 2001;280(2):H509-21.
15. Lambert GP. Intestinal barrier dysfunction, endotoxemia, and gastrointestinal symptoms: the 'canary in the coal mine' during exercise-heat stress? Med Sport Sci 2008;53:61-73.
16. Wang Y, Li D, Wu Z, et al. Development and validation of a prognostic model of survival for classic heatstroke patients: a multicenter study. Sci Rep 2023;13(1):19265.
17. Tong HS, Liu YS, Wen Q, Tang YQ, Yuan FF, Su L. Serum procalcitonin predicting mortality in exertional heatstroke. Emerg Med J 2012;29(2):113-7.
18. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. Lancet 1993;341(8844):515-8.
19. Tau ME, Cocca M. Misleading Serum Procalcitonin Elevation in Heatstroke. Eur J Case Rep Intern Med 2017;4(8):000695.
20. Clec'h C, Ferriere F, Karoubi P, et al. Diagnostic and prognostic value of procalcitonin in patients with septic shock. Crit Care Med 2004;32(5):1166-9.
21. Charles PE, Tinel C, Barbar S, et al. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. Crit Care 2009;13(2):R38.
22. Hausfater P, Hurtado M, Pease S, et al. Is procalcitonin a marker of critical illness in heatstroke? Intensive Care Med Aug 2008;34(8):1377-83.

熱中暑與橫紋肌溶解中的血清降鈣素原：診斷陷阱與預後潛力

郭金和[1] 林信安[2] 陳建州[3,4]

[1]三軍總醫院松山分院心臟內科
[2]三軍總醫院松山分院感染科
[3]三軍總醫院松山分院腎臟科
[4]國防醫學大學內科學科

摘要

熱中暑是一種危及生命的急症，特徵為核心體溫升高與全身性發炎反應，常導致多重器官功能障礙。運動型熱中暑 (EHS) 主要影響年輕活躍族群，常併發橫紋肌溶解症 (RM)，其特徵為骨骼肌崩解並釋放細胞內容物進入血液循環，此過程可引發無菌性發炎反應，臨床表現與細菌性敗血症高度相似，造成診斷上的困難。血清降鈣素原 (PCT) 作為細菌感染與敗血症的生物標記已有廣泛應用，然而在創傷、燒傷及熱相關疾病等非感染性情境中也可能顯著升高。在 EHS 合併 RM 的情況下，PCT 升高更可能反映全身性發炎反應與組織損傷的程度，而非真正感染的存在。若錯誤解讀 PCT 值，可能導致不當使用抗生素及病人照護策略錯置。本綜述整合目前關於 RM 與 PCT 在熱損傷情境下的研究證據，重點討論 PCT 升高的病理生理機制、其在感染鑑別上的侷限性，以及其作為預後指標的潛力。臨床醫師應結合臨床表現、PCT 變化趨勢及其他輔助檢查來提高診斷準確度，並導引適當的治療決策。