Endocrine aspects of critical illness
Conséquences endocriniennes des états critiques

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Abstract

Metabolic disorders and endocrine changes are common and relevant in critically ill patients. Thereby, endocrinopathies, electrolyte or metabolic derangements may either pre-exist or develop, and left unattended, may lead to significant morbidity and mortality. The homeostatic corrections which have emerged in the course of human evolution to cope with the catastrophic events during critical illness involve a complex multisystem endeavour, of which the endocrine contribution is an integral component. Although the repertoire of endocrine changes has been probed in some detail, discerning the vulnerabilities and failures of this system is far more challenging. The ensuing endocrine topics illustrate some of the current issues reflecting attempts to gain an improved insight and clinical outcome for critical illness. Disturbances in glucose and cortisol homeostasis during critical illness are two controversially debated topics in the current literature. The term “hormokine” encompasses the cytokine like behaviour of hormones during inflammation and infections. The concept is based on an ubiquitous expression of calcitonin peptides during sepsis. Adrenomedullin, another member of the calcitonin peptide superfamily, was shown to complement and improve the current prognostic assessment in lower respiratory tract infections. Procalcitonin is the prototype of “hormokine” mediators circulating procalcitonin levels increase several 10 000-fold during sepsis improve the clinical assessment especially of respiratory tract infections and sepsis safely and markedly reduces antibiotic usage in non-bacterial respiratory tract infections and meningitis. Adrenomedullin, another member of the calcitonin peptide superfamily, was shown to complement and improve the current prognostic assessment in lower respiratory tract infections. Hormokines are not only biomarkers of infection. Hormokines are also pivotal inflammatory mediators. Like all mediators, their role during systemic infections is basically beneficial, possibly to combat invading microbes. Yet, with increasing levels they can become harmful for their host. Multiple mechanisms of action were proposed. In several animal models the modulation and neutralization of hormokines during infection was shown to improve survival and thus might open new treatment options for severe infections, especially of the respiratory tract.

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Of course, “critical illness” is not a simple disease entity, and scanning the literature one cannot evade the impression that this fact is sometimes neglected. Inducers of life-threatening “critical” stress include trauma, burns, surgery, infections, and multiple other diseases typically associated with variable levels of inflammation [1]. The hormonal profile during these very distinct diseases varies substantially [2]. Although for didactic purposes unavoidable, any attempt to summarize hormonal changes during so-called “critical illness” is oversimplistic and, thus, inherently problematic. These caveats need to born in mind before drawing heroic therapeutic implications from allegedly promising hypothesis for a disease syndrome in the absence of unequivocal scientific evidence.

1. Hyperglycemia in diabetic and in previously non-diabetic individuals

Importantly, also in previously non-diabetic patients, the occurrence of acute hyperglycemia during critical illness has been shown to correlate with adverse outcome [3], stressing the importance of precise glucose control in any patient admitted to a surgical intensive care unit (ICU). Critical illness and/or severe surgical stress trigger a metabolic response which invariably causes a transient increase in plasma glucose concentrations, or stress hyperglycemia. Its occurrence is an ubiquitous finding in ICUs, with almost 75% of previously non-
appropriate adaptation of the hypothalamic-pituitary-adrenal (HPA) axis to stress is essential for survival [11,12]. Increasing circulatory levels of adrenal steroids (e.g. cortisol), are the consequence of an acutely and markedly activated anterior pituitary (i.e. adrenocorticotropic hormone, ACTH) and hypothalamic (e.g. corticotropin-releasing hormone, CRH, and vasopressin, also termed anti-diuretic hormone, ADH) response [13]. This happens under the influence of higher cortical functions, spinal and peripheral baroreceptors, among others. Thereby, the acute stress response gets adapted throughout the course of critical illness [14]. In addition, disease-related variations in the binding capacities of circulating proteins (namely cortisol binding globulin and albumin) result in even more fluctuating levels of free stress hormones during critical illness [15–19]. The tissue and cellular responses to free circulating hormone levels further vary substantially on the receptor and post-receptor levels [20–24]. The half life of cortisol in the blood is increased during stress, due to a decreased rate of hepatic extraction and renal enzymatic inactivation of cortisol to cortisone by the 11β-hydroxysteroiddehydrogenase, respectively, [25]. Finally, the immuno-neuro-endocrine interactions are bidirectional, both mutually potentiating and attenuating and not fortuitous. Several gluco- and mineralo-corticoids modulate the immune response distinctively [26]. On the other hand, cytokines (e.g. tumour necrosis factor (TNF), interleukins (Ils) and macrophage-migration inhibitory factor, MIF) and bacterial products (e.g. endotoxin) are able to modulate the response of the HPA axis at each level (summarized in [10]).

Cortisol (also termed hydrocortisone or Compound F) is considered the “primary”, active glucocorticoid and is essential for the adaptation and maintenance of stress homeostasis during critical illness [27–29]. Characteristically, any acute insult will result in an augmented release of cortisol and other adrenal steroids, among other factors mediated by a sharp rise of circulating short-lived ACTH, which in turn is driven by CRH, vasopressin, cytokines, and an upregulated noradrenergic system, just to name a few [14]. The production of cortisol in the adrenocortical cells in response to ACTH occurs within minutes and begins with the enzymatic cleavage of the side chain of cholesterol to generate pregnenolone and, by additional enzyme systems, cortisol [30,31]. Thereby, the normal feedback system might be altered as hypercortisolism is less suppressible by dexamethasone infusion in septic shock. [32]. Moreover, the normal circadian rhythm of cortisol secretion, especially the nadir during night-time, is disturbed [33,34]. Reported plasma hormone levels vary widely among studies. The persistence of pulsatile secretion may explain the observed variability and, accordingly, the accuracy of single samples is potentially inadequate, as for all hormones [35]. Furthermore, the inter-individual and inter-assay variability of different cortisol and other steroid assays measuring free or total hormone concentrations at different sites and centres can be substantial [15,36–38].

Although the rennin-angiotensin–aldosterone system is also activated [39], the acute adaptive adrenal response to stress is typically seen as a shift from mineralocorticoid production to a more marked increase in glucocorticoid production. In addition, in acute illness the biological effects of cortisol increase
due to a decrease in cortisol binding globulin (CBG) and an increase in receptor sensitivity and number [10,19].

Increased circulating cortisol levels seem to reflect an increasing severity of illness [40,41], and mortality of untreated adrenal insufficiency increases with the severity of the acute stress [42]. Similarly, peri- and post-operative basal cortisol concentrations reflect the degree of surgical stress [43,44]. Peak cortisol levels are achieved in the immediate postoperative period, around extubation [45,46]. Cortisol levels after major surgery resemble the levels during the acute phase of septic shock [40,47,48]. While in the acute phase of critical illness the secretory activity of the HPA axis is essentially maintained or augmented, it starts to diminish during the chronic phase, i.e. after a few weeks of protracted critical illness [40,49].

The terms “relative” or “functional” adrenal insufficiency have been proposed for hypotensive, septic critically ill patients who show hemodynamic improvement upon cortisol administration. In these patients, the cortisol levels — despite being within the normal reference range or even elevated — are still considered to be inadequate for the severity of stress, and the patient may be unable to respond to any additional or protracted stress [50]. Corticosteroid insufficiency is difficult to discern clinically and must be actively sought by the treating physician. There are no clinical indicators (e.g. eosinophilia, vasopressor dependence or hemodynamic response) with proven diagnostic accuracy, partly because of a lack of a reference standard [51,52]. The life-threatening dangers of stress in untreated absolute adrenal insufficiency are undisputable. In contrast, there is a debate concerning the definition of relative adrenal insufficiency, its treatment and the identification of patients at risk [10,50,51,53,54].

A simple and widely used test is the stimulation of cortisol with injection of synthetic ACTH (Synacthen®) in hypotensive critically-ill patients. Thereby, a “basal” cortisol of > 935 nmol/l combined with an increase (Δ) of cortisol < 250 nmol/l (9 μg/dl) after stimulation with 250 μg ACTH has been associated with a mortality of 80% arguably pointing to a relative adrenal insufficiency [40]. However, circulating ACTH levels after a standard injection of 250 μg ACTH are extremely high (10’000–60’000 pg/ml) and much higher than the 100–300 pg/ml found after stimulation with 1 μg synthetic ACTH [48,51,55]. Since the 250 μg ACTH stimulation test induces supraphysiological ACTH concentrations, the 1 μg synthetic ACTH test has been suggested to be more sensitive to diagnose adrenocortical insufficiency [56]. In healthy individuals, one microgram is the lowest ACTH dose to cause a maximal cortisol response and there is no diurnal variation of cortisol response to submaximal ACTH stimulation [56]. However, there is a stress-dependent dissociation of the cortisol response to increasing doses of synthetic ACTH in situations of stress, as shown during strong surgical stress [41]. Accordingly, in stressed patients without HPA disease cortisol concentrations are higher after stimulation with 250 μg as compared to 1 μg ACTH. Thus, the adrenal reserve is not completely utilized and is not the limiting organ in this model of strong surgical stress.

What do we really measure with adrenal stimulation tests [51,57]? Is an additional rise in cortisol upon ACTH-stimulation of any clinical significance, namely the arguably decisive increment (Δ) in serum cortisol concentration of 250 nM (9 μg/dl) from baseline? [58] In the study of Widmer et al. about 40% of surgical patients did not achieve this target Δ cortisol, yet none of them suffered any adverse clinical consequences from severe surgical stress without glucocorticoid substitution [41]. Indeed, in the setting of severe illness and stress the use of the low-dose (1ug) ACTH stimulation test may increase the number of over-diagnosed patients [59,60]. Because of the circadian rhythm in healthy individuals basal cortisol levels are lower in the evening than in the morning, yet the stimulated cortisol levels will be similar. This is true regardless of whether the stimulation is performed by using ACTH [61], insulin hypoglycaemia [62], metyrapone [63], or CRH [64]. Therefore, the incremental rise (Δ) of cortisol is inherently negatively correlated with basal cortisol levels and, thus, not a useful parameter. Furthermore, the inter-individual variability of different cortisol and other steroid hormone assays performed at different sites can be substantial [36]. This calls for a complete rethinking of the term “relative adrenal insufficiency” [57].

Whether “iatrogenic” hypercortisolism during critical illness is truly needed and beneficial remains uncertain. Even a continuous, intended-to-be-physiological “low-dose” infusion of hydrocortisone results in several fold higher levels (up to 3000–5000 nM) as compared to maximal endogenous hypercortisolism reached during severest near-death stress in patients with intact adrenal reserve [65,66]. Concerning treatment of relative adrenal insufficiency in patients with septic shock, one single larger trial found a reduction of mortality, however, only post-hoc in the subgroup of patients with impaired rise (Δ) of cortisol < 250 nM (< 9 μg/dl) 30 min after the injection of 250 μg synthetic ACTH [58]. Interestingly, previously published criteria for the prognostic characterization of critical illness from the same group were not considered [40]. The large confidence interval of pre- and post-stimulation cortisol levels in this study tell us, that patients were very heterogeneous and clearly included a sizable number of patients with true “absolute” adrenal insufficiency, potentially skewing results [67]. Furthermore, in contrast to all other studies, in this trial oral fludrocortisone was added to the intravenous administration of hydrocortisone [58]. The administration of tablets in critically ill patients may be cumbersome and, therefore, fludrocortisone is often omitted in routine intensive care. Unfortunately, as the authors of this study state, there was “no interest in formally demonstrating a deleterious effect of corticosteroids” [58]. Suggesting thereafter that corticosteroids do not have potential for harm in critically ill septic patients is untenable [68]. Despite these limitations, this study had a land-slide impact on the management of critically ill patients, not only with vasopressor-refractory septic shock, but, unfortunately and albeit unproven, also to other “therapy-refractory” ICU patients with milder or even without infections. Possibly, the administration of steroids was so welcomed and became fashionable because the time had come resurrect past rites. In the
context of such controversy, the premature publication of preliminary data from small, under-powered studies in high-impact journals is of little help [69]. Some intensivists argue that a hemodynamic improvement can be observed after the administration of “stress doses” (i.e. 50 to 200 mg) of hydrocortisone. This would justify its administration to reduce the per se harmful doses of catecholamines needed to maintain blood pressure. However, in this context the question was raised if we should use hydrocortisone as a therapy to improve our charts or the outcome of our patients [70].

Multiple studies were performed by opinion leaders from both sides, not surprisingly yielding opposite conclusions especially with regards to dosing of the steroids and the interpretations of the Δ cortisol after ACTH-stimulation [51,71–76]. In this field, the comparison of different studies in systematic reviews and meta-analyses is inherently problematic as largely patient groups included differ widely in terms of underlying diagnosis (e.g. patients suffering from infections, acute lung injury, acute respiratory distress syndrome, burns, malaria, and others), inclusion criteria (e.g. all consecutive patients versus subgroups of selected patients, different severities of infection varying from sepsis, severe sepsis to refractory septic shock), and the timing of inclusion (on admission, during the early phase of critical illness and during the course of disease after failing to respond to other supportive interventions like the administration of fluids and catecholamines). In part, patients were post-hoc dichotomized based on an allegedly inadequate response in the ACTH stimulation test [58] and/or “basal” cortisol levels [67]. Finally, the remedies tested were very diverse and included hydrocortisone [75], methylprednisolone [77], dexamethasone [78], fludrocortisone [58], and even DHEA [79–81], in part combined and among others. Circulating half-life (T1/2), biological effects and the potency of these drugs varies widely. Similarly, the correlation between a given circulating T1/2 of a glucocorticoid and its duration of action is poor [28]. Dosages applied in critically ill patients ranged from so-called “supra-physiological” [75], to “low-dose” [58] and to “high dose” [77,78]. Of course, the use of these terms is not validated given the fact that we are unable to determine and monitor the true needs for a given individual with a specific critical disease at a certain time point. Importantly, all the different steroids administered, have markedly distinct biological effects, which is self-evident based on their variable structure. Only subtle differences in the biochemistry of steroid hormones can alter the biologic response dramatically. Take a look at the “male” hormone testosterone and the “female” hormone estradiol. The only difference between those two steroid molecules is the interchangeable oxidation of a hydroxyl side group. Nevertheless, phenotypic differences between both sexes can be rather impressive. In this context, the differences between the steroids used therapeutically in critical illness, including but not limited to glucocorticoids and mineralocorticoids, are even more important and should not be neglected.

Upon cessation, any short or long-term exposure to “supraphyisiological” glucocorticoid dosages will expose the patients subsequently to the risk of “absolute” insufficiency of the HPA-axis, i.e. Addison’s Syndrome. This iatrogenic complication can be life-threatening, namely in stress situations (e.g. recurrence of the critical illness). Rapid restoration of ACTH release with CRH infusion suggests that the suppression of the HPA-axis after iatrogenic hypercortisolism is predominantly due to reduced CRH secretion [82]. The extent and duration of this functional deficiency is unpredictable, may last from weeks to years and is largely independent of the dose and duration of steroid therapy, respectively [83,84]. This has led to the conservative practice of replacing glucocorticoid before an anticipated stress in any patient who has received supraphysiological dosages of glucocorticoids within the past year [29,85].

Today, there is little definitive advice to offer concerning the use of pharmacological doses of glucocorticoids in critical illness in general, especially in critically ill patients who do not meet the criteria for "relative adrenal insufficiency". The alleged benefits should be weighed against the proven dangers of such therapy, such as hyperglycemia [7,86] and a suppression of the immune response [73,77,87–89]. For example, in comatose patients with cerebral malaria, high-dose dexamethasone treatment has been proven deleterious [90]. Importantly, the ebb and flow of attitudes regarding the usefulness of large-dose steroid treatment in spinal cord injured patients, also referred to as “CRASH-landing of steroids” based on the acronym of a seminal study, is a case in point [91–93]. The clinical frustrations of dealing with severe sepsis and its high mortality rate may tempt many clinicians to use corticosteroids. However, our urge to do something should not tempt us to do anything. Adhering to the results of current randomized controlled trials is the best current guide when applying these to clinical practice. More rigorously controlled multicenter studies are required to further clarify this complex clinical enigma. The ongoing “CORTICUS” study is one of them and intensivists anxiously await the publication of this trial, where cortisol administration allegedly did not result in any benefit [94].

3. Calcitonin peptides: marker and mediators in infections

Calcitonin was discovered 40 years ago, when it was assumed to be a single hormone with an unknown role in human physiology [95,96]. Since then, it has been found to be only one entity among related circulating peptides which have pivotal roles in the metabolic and inflammatory host response to microbial infections [97]. Calcitonin peptides share their origin from a common ancestral gene (the “CALC”-gene) and have pronounced structural homologies. They include PCT, CGRP I and II, adrenomedullin, and amylin and their respective precursor peptides. With the exception of amylin, serum concentrations of all CT-peptides are increased to variable extents during inflammation and infection [98–100]. PCT is a precursor peptide from the hormone calcitonin, and is also referred to as being the prototype of “hormokines” mediators [101].

Calcitonin gene products (e.g. procalcitonin (PCT), CT gene-related peptides (CGRPs) and adrenomedullin) are a prototype of hormokine mediators: they can follow either a classi-
onical hormonal expression in neuroendocrine cells or, alternatively, a cytokine-like ubiquitous expression pathway in various cell types [97,102–105]. Thereby, the inflammatory release can be induced either directly via microbial toxins (e.g. endotoxin) or indirectly via a humoral or cell-mediated host response (e.g. IL-1β, TNF-α, IL-6). Parenchymal cells (including liver, kidney, adipocytes and muscle) provide the largest tissue mass and principal source of circulating hormones in sepsis. Lowering of circulating hormones by specific antibodies or small competing molecules improves survival in various animal models, in different severities and time-points of mono- and polymicrobial sepsis [106,107].

Mortality in sepsis remains high, often due to delayed diagnosis and treatment. The traditional clinical signs of infection and the routine laboratory tests in sepsis (e.g. C-reactive protein [CRP] or white blood cell count) lack diagnostic accuracy and are sometimes misleading. In severe infection, most classical proinflammatory cytokines (e.g. TNF-α, IL-1β or IL-6) are increased only briefly or intermittently, if at all. In view of this diagnostic and therapeutic dilemma, a more unequivocal test for the differential diagnosis of infection and sepsis is of paramount importance. Recently, in an attempt to improve current definitions of SIRS and sepsis, it was suggested to include PCT as additional diagnostic tool to improve and expedite the difficult clinical diagnosis [108]. This was also based on evidence from the literature that in sepsis, PCT levels increase several-fold until several thousand-fold and on admission this increase often correlates with the severity of the condition and with subsequent mortality [109]. A variety of studies and reviews have shown the superior diagnostic accuracy of PCT as compared to other parameters for the diagnosis of sepsis, independent of the origin of infection [109]. Whereas the increase of other inflammatory markers such as CRP is attenuated by immunosuppressive medication (namely steroids), the diagnostic accuracy of PCT remains unaffected [89]. In addition, PCT seems to have a slight advantage over CRP because of its earlier increase upon infection and a better negative predictive value, as for example shown in children with fever of unknown origin [110] and adult patients with systemic inflammatory response in critical illness [111], trauma and surgery [112]. In a French pilot-study a blood PCT level < 0.5 ng/mL was prospectively used for the diagnosis of viral origin of meningitis in 58 patients (2 months and 14 years), in which enterovirus was isolated by culture or PCR during an outbreak (May-June 2000). Seventeen patients and 14 years), in which enterovirus was isolated by culture or PCR during an outbreak (May-June 2000). Seventeen patients received antibiotic therapy in admission. PCT dosage was routinely measured three times per week with the LUMItest. In nine patients, a PCT result < 0.5 ng/mL was obtained in 24 h and in 48 h in six: treatment was then stopped and children left hospital. Thus, PCT dosage allowed shortening of hospitalization and reducing of unnecessary antibiotic treatments. This study is important but was not powered to address the safety and external validity for widespread use. [113].

The most frequent source of severe systemic infections is lower respiratory tract infections [100]. A common problem in clinical practice is that, similar to sepsis, in respiratory tract infections, signs and symptoms of bacterial and viral infections are widely overlapping. After obtaining the medical history, physical examination, laboratory, and chest X-ray, the clinician is often left with considerable diagnostic uncertainty. In view of this diagnostic and therapeutic dilemma, a more reliable test for the differential diagnosis of bacterial respiratory tract infections in need for antibiotics from other respiratory disease would be extremely helpful [114].

Over the past years we, therefore, investigated the ability of PCT and other hormones used as biomarkers to improve the clinical diagnosis, the prognostic assessment and therapeutic management of respiratory tract infections.

For procalcitonin, and only for this marker, this has been shown in four intervention trials enrolling more than 1250 patients with respiratory tract infections, including co-morbid, critically ill and septic patients. The vast majority of eligible patients agreed to participate in those intervention studies, assuring applicability under “real life” conditions. Briefly, use of antibiotics was more or less discouraged (< 0·1 ug/L or < 0·25 ug/L) or encouraged (>0·5 ug/L or >0·25 ug/L) based on a range of procalcitonin levels. In the ProRESP study, procalcitonin-guidance reduced AB use in 243 patients with lower respiratory tract infections by almost 50% [115]. In the ProCAP study, procalcitonin-guided antibiotic duration was shortened by 65% from 12.9 to 5.8 days in over 300 patients with mostly severe community acquired-pneumonia [116]. In the ProCOLD-study long-term safety of this approach was shown with a similar readmission rate over 6 months in over 200 acute exacerbations of chronic obstructive lung disease [117]. In the PARTI-study procalcitonin-guidance safely reduced antibiotic exposure by 75% enrolling more than 450 patients in primary care. (([118] and data on file).

In patients with CAP, improved diagnostic assessment by PCT is important to differentiate from other, non-infectious infiltrates, and to guide the duration of antibiotics. In addition, it is pivotal to being able to predict the prognosis of CAP and to estimate CAP severity for guiding therapeutic options such as the need for hospital or intensive care admission, suitability for discharge and choice and route of antimicrobial agents. Again, despite their widespread use in clinical routine traditional markers such as severity of disease assessment by the patient, fever, white blood cell count and also CRP are not reliable to assess disease severity and mortality risk in CAP. The pneumonia severity index (PSI) is a widely accepted and validated severity scoring system that assesses the risk of mortality for pneumonia patients in a two-step algorithm combining clinical signs, demographic data and laboratory values [119]. However, its complexity is high, jeopardizing its dissemination and implementation especially in everyday’s practice. Therefore, the CURB-65 score has been proposed as a simpler alternative.

The dynamics of PCT levels have prognostic implications, as persistently elevated levels are associated with adverse outcome [120]. Conversely, decreasing PCT levels suggest a favourable outcome, usually showing a log-linear drop-off and a half life of 20–24 h [97]. The prognostic accuracy of PCT in the ICU can be markedly improved considering the course of PCT [121]. Jensen et al. analyzed a total of 3642
PCT measurements in 472 critically ill patients. The absolute PCT level, but especially the PCT-increase for one day was an independent predictor of 90-day all-cause mortality in the multivariate Cox regression analysis model. The adjusted hazard ratio for PCT increase for 1 day was 1.8 (95% CI 1.3–2.7) and the Relative Risk for mortality in the ICU for patients with an increasing PCT, was after one days increase: 1.8 (95% CI 1.4–2.4), after 2 days increase: 2.2 (95% CI 1.6–3.0) and after 3 days increase: 2.8 (95% CI 2.0–3.8). Thus, a PCT-increase during the course of disease was an independent predictor of all-cause mortality in a 90-day follow-up period after ICU admission. Mortality increased with every day PCT is increasing. Levels of increases in CRP and white blood cell count did not seem to predict mortality. In our studies, PCT also showed a better prognostic accuracy compared to routinely measured parameters like CRP or leukocyte count and has therefore been proposed as a marker of disease severity [122,123]. However, there was a wide overlap in PCT levels between different severities of CAP and only a small difference in PCT levels between survivors and non-survivors of CAP. Based on these data, PCT seems to be rather a reliable diagnostic marker able to guide decisions on antibiotic therapy and not an ideal prognostic tool [123,124].

Another member of the CALC gene family is adrenomedullin. Adrenomedullin is one of the most potent vasodilating agents and has additional immune modulating, metabolic properties [104,125–127]. Adrenomedullin has also a bactericidal activity which is further enhanced by modulation of complement activity and regulation. Thus, it is not surprising that serum adrenomedullin levels were found elevated in sepsis [128]. The reliable measurement of adrenomedullin is challenging, since it is rapidly cleared from the circulation [125,126]. The more stable mid regional fragment of pro-adrenomedullin directly reflects levels of the rapidly degraded active peptide adrenomedullin [129].

In our study in over 300 patients with CAP, proadrenomedullin levels measured on admission emerged as good predictors of severity and outcome of CAP with a similar prognostic accuracy as compared to the PSI and a better prognostic accuracy as compared to commonly measured clinical and laboratory parameters. Importantly, proadrenomedullin levels could improve the prognostic accuracy of the PSI alone, acting as an additional margin of safety [123].

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