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PREGLEDNI RAD

ENDOKRINE I IMUNOLOŠKE PROMENE U TEŠKOJ TRAUMI: SAVREMENI BIOMARKERI, PROGNOSTIČKI FAKTORI I KLINIČKE IMPLIKACIJE

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SAŽETAK

Teška trauma pokreće složen i dinamičan odgovor organizma koji obuhvata istovremene endokrine, imunološke i metaboličke promene, sa direktnim uticajem na klinički tok i ishod lečenja. Aktivacija hipotalamo–hipofizno–adrenalne ose, promene u lučenju kateholamina, poremećaji tireoidne funkcije i disbalans inflamatornog odgovora predstavljaju ključne komponente sistemskog odgovora na traumatski stres. Cilj ovog preglednog rada bio je da se, na osnovu savremene literature, sistematizuju endokrini i imunološki biomarkeri koji imaju prognostički značaj kod pacijenata sa teškom traumom, kao i da se sagledaju njihove kliničke implikacije u intenzivnoj medicini. Pregledom relevantnih radova objavljenih u periodu od 2014. do 2025. godine analizirane su promene koncentracija kortizola i kateholamina, sindrom insuficijencije kortikosteroida povezan sa kritičnom bolešću (CIRCI), ne-tiroidni sindrom bolesti (NTIS), kao i inflamatorni biomarkeri poput interleukina-6 i C-reaktivnog proteina. Posebna pažnja posvećena je njihovoj ulozi u predikciji mortaliteta, razvoja multiple organske disfunkcije, respiratornog pogoršanja i septičkih komplikacija. Dostupni podaci ukazuju da rani poremećaji endokrinih osa, naročito abnormalni obrasci kortizolne i tireoidne reakcije, imaju značajnu prognostičku vrednost, dok inflamatorni i transkriptomski biomarkeri omogućavaju precizniju stratifikaciju rizika u ranim fazama kritične bolesti. Integracija endokrinih, imunoloških i metaboličkih biomarkera sa kliničkim parametrima i demografskim karakteristikama pacijenata predstavlja osnovu savremenog, personalizovanog pristupa u lečenju teške traume. Dalja istraživanja treba da budu usmerena ka standardizaciji dijagnostičkih kriterijuma, optimalnom vremenu uzorkovanja i evaluaciji terapijskih intervencija, sa ciljem unapređenja ishoda i smanjenja mortaliteta kod kritično obolelih pacijenata.

Ključne reči: trauma, rendokrini biomarkeri, imunološki biomarkeri, prognoza, kritično stanje

Uvod

Trauma je vodeći uzrok smrtnosti kod mladih odraslih, a komplikacije kritičnih stanja nakon teške traume predstavljaju izazov u akutnoj medicini (1,2). Teška trauma izaziva složenu kaskadu endokrinih, metaboličkih i imunoloških odgovora, koji imaju direktan uticaj na klinički ishod (3-6). Hormonske promene uključuju povećanu sekreciju kortizola, kateholamina i poremećaje tireoidnog sistema, dok imunološki odgovor obuhvata proinflamatorne i antiinflamatorne mehanizme koji moduliraju rizik od multiple organske disfunkcije i sepse (7-9).

Razumevanje ovih biomarkera i njihove prediktivne vrednosti može unaprediti ranu identifikaciju pacijenata sa visokim rizikom od komplikacija, optimizovati terapijske strategije i poboljšati ishod pacijenata (3,10,11). Cilj ovog preglednog rada je bio da na osnovu dostupne literature sumira trenutna saznanja o endokrinim i imunološkim promenama kod teške traume, njihovoj prognostičkoj vrednosti i kliničkim implikacijama.

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REVIEW ARTICLE

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ENDOCRINE AND IMMUNOLOGICAL ALTERATIONS IN SEVERE TRAUMA: CONTEMPORARY BIOMARKERS, PROGNOSTIC FACTORS, AND CLINICAL IMPLICATIONS

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SUMMARY

Severe trauma triggers a complex and dynamic response of the organism that includes simultaneous endocrine, immunological and metabolic alterations with a direct impact on the clinical course and treatment outcome. Hypothalamic-Pituitary-Adrenal (HPA) axis activation, changes in the secretion of catecholamine, disorders of the thyroid function and imbalance of the inflammatory response are key components of the systemic response to traumatic stress. The aim of this review article was to systematize endocrine and immunological biomarkers that have prognostic relevance in patients with severe trauma based on contemporary literature, as well as to review their clinical implications in intensive care medicine. Relevant papers published in the period 2014 to 2025 were reviewed in order to analyze changes in cortisol and catecholamine concentrations, Critical Illness-related Corticosteroid Insufficiency (CIRCI) Syndrome, Non-Thyroid Illness Syndrome (NTIS), as well as inflammatory biomarkers such as Interleukin-6 and C-reactive protein. Special attention was paid to their role in predicting mortality, development of multiple organ dysfunction, respiratory deterioration and septic complications. Available data indicate that early disorders of endocrine axes, especially abnormal patterns of cortisol and thyroid reactions have a significant prognostic values, while inflammatory and transcriptomic biomarkers allow more precise risk stratification in the early stages of critical disease. The integration of endocrine, immunological and metabolic biomarkers with clinical parameters and demographic characteristics of patients is the basis of a modern, personalized approach in the treatment of severe trauma. Further research should be directed towards standardization of diagnostic criteria, optimal sampling time and evaluation of therapeutic interventions, with the aim of improving outcomes and reducing mortality in critically ill patients.
Key words: trauma, endocrine biomarkers, immunological biomarkers, prognosis, critical condition

Introduction

Trauma is the leading cause of mortality in young adults, and complications of critical conditions after severe trauma are a challenge in acute medicine (1,2). Severe trauma triggers a complex cascade of endocrine, metabolic and immune responses, which have a direct impact on clinical outcome (3-6). Hormonal changes include the increased secretion of cortisol, catecholamine, and disorders of the thyroid system, while the immune response includes pro-inflammatory and anti-inflammatory mechanisms that modulate the risk of multiple organ dysfunction and sepsis (7-9).

Understanding these biomarkers and their predictive value can improve the early identification of patients at high risk of complications, optimize therapeutic strategies, and improve patient outcomes (3,10,11). The aim of this review article was to summarize current knowledge about endocrine and immunological changes in severe trauma, their

Metode

U okviru ovog preglednog rada pretražene su baze podataka kao što su PubMed, Web of Science i Scopus, a za pretraživanje korišćene su sledeć ključne reči: *trauma, critical illness, cortisol, catecholamines, thyroid hormones, CIRCI, NTIS, immune response, biomarkers, prognosis*. Uključeni su radovi objavljeni između 2014. i 2025. godine, na engleskom jeziku, koji se bave hormonalnim i imunološkim odgovorom na traumu, predikcijom ishoda i kliničkim implikacijama. Radovi su kategorisani po temama: hormonski odgovor, tireoidni poremećaji, CIRCI, imunološki biomarkeri i predikcija ishoda. Prikazani su originalni istraživački radovi, sistematski pregledi, meta-analize i narativni pregledi.

Diskusija

Teška trauma izaziva kompleksnu mrežu hormonskih i imunoloških promena, koje su usko povezane sa kliničkim ishodom kod pacijenta. Analizom 23 relevantna rada identifikovano je nekoliko ključnih oblasti: hormonski stresni odgovor (kortizol i kateholamini), poremećaji tireoidnog sistema (NTIS), insuficijencija kortikosteroida povezana sa kritičnom bolešću **(**CIRCI), inflamatorni i imunološki biomarkeri, kao i prediktivni faktori mortaliteta i komplikacija.

Kortizol i hormonski stresni odgovor

Kortizol predstavlja jedan od ključnih hormona u akutnom endokrinom odgovoru na traumatski stres, reflektujući aktivaciju hipotalamo-hipofizno-adrenalne (HHA) osovine i intenzitet sistemskog fiziološkog opterećenja organizma. Njegova dinamika u prvih nekoliko sati do dana nakon povrede pokazala se klinički relevantnom u više istraživanja različitih populacija traume i hirurških pacijenata. Kwok i saradnici (3) sproveli su prospektivnu evaluaciju koncentracija kortizola pri prijemu kod pacijenata sa traumom i pokazali da je rani hormonski odgovor snažan marker inicijalnog fiziološkog stresa. U njihovoj kohorti, pacijenti sa povišenim početnim nivoima kortizola imali su izraženije poremećaje hemodinamske stabilnosti, veću verovatnoću razvoja rane posttraumatske insuficijencije organa i duži boravak u jedinici intenzivne nege. Njihovi nalazi sugerišu da kortizol na prijemu ima ulogu ranog "biološkog barometra" težine traume, te može doprineti ranoj stratifikaciji rizika.

S druge strane, Goder i saradnici (10) analizirali su cirkulatorni kortizol tokom prvog dana hospitalizacije kod hirurški kritično obolelih pacijenata. Njihovi rezultati ukazuju da ne samo apsolutni nivoi, već i obrazac promena kortizola unutar prvih 24h nose prognostičku vrednost – pacijenti sa perzistentno povišenim ili neadekvatno niskim odgovorom hormona imali su nepovoljnije ishode, uključujući produženu mehaničku ventilaciju, višu učestalost komplikacija i lošiju ukupnu prognozu. Ova studija naglašava važnost praćenja hormonske reaktivnosti u akutnoj fazi, budući da ona odražava efikasnost adaptacionih mehanizama i funkcionalni integritet HHA-ose kod teško obolelih pacijenata.

Meta-analiza koju su sproveli Engel i saradnici (4) dodatno osvetljava ulogu kortizola kao prediktora psiholoških posledica traume. Analizirajući eksperimentalne modele traume i praćenje psiholoških ishoda, autori pokazuju da intenzitet i vreme kada nivo kortizola dostigne svoj maksimum mogu imati prediktivni značaj za kasniji razvoj simptoma posttraumatskog stresnog poremećaja (PTSP). Ipak, ova meta-analiza ukazuje na značajnu heterogenost usled razlika u dizajnu studija, metodologiji indukcije stresa, tipu biološkog materijala (serum, pljuvačka) i različitim referentnim vremenskim tačkama, što dovodi do varijabilnosti nalaza među radovima.

Dodatne informacije o tome kako telo luči kortizol dobijamo iz pregleda studija koje su se bavile stresom organizma tokom operacija. Prete i saradnici (6), kroz obimnu sistematsku analizu, opisuju da hirurška intervencija predstavlja snažan stresor koji aktivira predvidivu, ali individualno varijabilnu korzizolsku. Njihov pregled ukazuje da obim i tip operacije, prethodno zdravstveno stanje pacijenta, zapaljenski status i anesteziološke strategije značajno utiču na visinu i tok postoperativnog kortizolskog odgovora. Slično tome, narativni pregled Menger i saradnika (11) fokusiran na muskuloskeletnu hirurgiju potvrđuje da nivo kortizola pouzdano prati intenzitet operativnog stresa i postoperativnog metaboličkog opterećenja, pri čemu autori navode da individualne razlike u neuroendokrinom odgovoru mogu biti od kliničke važnosti za planiranje perioperativne brige i identifikaciju pacijenata sa visokim rizikom.

Integracijom svih ovih nalaza postaje jasno da kortizol predstavlja dinamičan, multifunkcionalan marker koji može reflektovati i somatske i psihološke aspekte traumatskog odgovora. Iako više pregleda i meta-analiza (4,6,11) potvrđuju njegov prognostički potencijal u predviđanju razvoja PTSP-a, kao i perioperativnih i posttraumatskih ishoda, postoje metodološka ograničenja koja utiču na konzistentnost rezultata, razlike u vremenu uzorkovanja, ma-

prognostic value and clinical implications based on the available literature.

Methods

Within this review article, databases such as PubMed, Web of Science and Scopus were searched and the following key words were used for the search: trauma, critical illness, cortisol, catecholamine, thyroid hormones, CIRCI, NTIS, immune response, biomarkers, prognosis. Papers published between 2014 and 2025 in the English language that dealt with the hormonal and immunological response to trauma, outcome prediction and clinical implications were included in the study. Papers were categorized according to themes: hormonal response, thyroid disorders, CIRCI, immunological biomarkers, and outcome prediction. Original research papers, systematic reviews, meta-analyses and narrative reviews were presented.

Discussion

Severe trauma causes a complex network of hormonal and immunological changes, which are closely related to the clinical outcome of the patient. The analysis of 23 relevant studies indentified several key areas: the hormonal stress response (cortisol and catecholamine), disorders of the thyroid system (NTIS), Critical Illness-related Corticosteroid Insufficiency (CIRCI), inflammatory and immunological biomarkers, as well as predictive factors of mortality and complications.

Cortisol and the hormonal stress response

Cortisol is one of the key hormones in the acute endocrine response to traumatic stress, reflecting the hypothalamic-Pituitary-Adrenal (HPA) axis activation, and the intensity of the systemic physiological load. Its dynamics in the first few hours to one day after injury have been shown to be clinically relevant in multiple studies of different populations of patients after trauma and surgical patients. *Kwok* et al. (3) conducted a prospective evaluation of cortisol concentrations in trauma patients upon hospital entry and demonstrated that the early hormonal response is a strong indicator of initial physiological stress. In their cohort, patients with elevated baseline cortisol levels had more pronounced disorders of hemodynamic stability, a higher likelihood of developing early post-traumatic organ failure, and a longer stay in the intensive care unit. Their findings suggest that admission cortisol has the role of the early "biological barometer" of trauma severity, and may contribute to early risk stratification.

On the other hand, *Goder* et al. (10) analyzed circulating cortisol during the first day of hospitalization in critically ill surgical patients. Their results indicate that that not only the absolute levels, but also the pattern of cortisol changes within the first 24h have a prognostic value – patients with a persistently elevated or inadequately low hormone response had less favorable outcomes, including prolonged mechanical ventilation, a higher frequency of complications and a worse overall prognosis. This study emphasizes the importance of monitoring hormonal reactivity in the acute phase, as it reflects the efficiency of adaptive mechanisms and the functional integrity of the HPA axis in critically ill patients.

A meta-analysis by *Engel et al.* (4) further clarifies the role of cortisol as a predictor of the psychological consequences of trauma. By analyzing the experimental models of traumas and monitoring psychological outcomes, the authors show that the intensity and time when cortisol levels reach their maximum may have predictive significance for later development of post-traumatic stress disorder (PTSD). However, this meta-analysis indicates significant heterogeneity due to differences in study design, methodology of stress induction, type of biological material (serum, saliva) and different reference time points, which leads to variability of findings between different studies.

Additional information about how the body secretes cortisol is obtained from a review of studies that dealt with the cortisol stress response induced by surgery. *Prete et al.* (6), through an extensive systematic analysis, describe that surgical intervention is a strong stressor that activates predictable, but individually variable cortisol response. Their review indicates that the extent and type of surgery, the patient's previous medical condition, inflammatory status, and anesthetic strategies significantly affect the levels and course of the postoperative cortisol response. Similarly, a narrative review by *Menger et al.* (11) that focused on musculoskeletal surgery confirms that cortisol levels reliably follow the intensity of surgical stress and postoperative metabolic load, while the authors state that individual differences in neuroendocrine response may be of clinical importance for planning perioperative care and identifying high-risk patients.

By integrating all these findings, it becomes clear that cortisol is a dynamic, multifunctional marker that can reflect both somatic and psychological aspects of the traumatic response. Although seve-

trici uzorka, definicijama ishoda i karakteristikama populacije. Uprkos ovim varijacijama, ukupna literatura dosledno ukazuje na to da je kortizol jedan od najpouzdanijih endokrinih pokazatelja akutnog stresa, sa značajnim kliničkim potencijalom u ranoj stratifikaciji rizika, praćenju adaptacionog odgovora i identifikovanju pacijenata sa povećanom verovatnoćom nepovoljnih ishoda, kako fizioloških, tako i psiholoških.

Sažeti prikaz ključnih endokrinih biomarkera, njihove patofiziološke uloge i prognostičkog značaja u teškoj traumi prikazan je u Tabeli 1.

Kateholamini i terapijske implikacije

Kateholamini, pre svega adrenalin i noradrenalin, predstavljaju ključne medijatore neuroendokrine adaptacije na hemoragijski šok, omogućavajući kratkoročno održavanje perfuzije vitalnih organa kroz povećanje srčane frekvencije, kontraktilnosti miokarda i sistemskog vaskularnog otpora. Međutim, ovaj kompenzatorni odgovor ima izraženu dvostruku fiziološku prirodu: iako je inicijalno zaštitni, prekomerno i prolongirano oslobađanje kateholamina povezano je sa pogoršanjem tkivne oksigenacije, metaboličkom acidozom i proinflamatornim odgovorom. Suh i saradnici (12) su pokazali da povišene koncentracije kateholamina kod hitno operisanih pacijenata snažno koreliraju sa mortalitetom, pri čemu povećane vrednosti noradrenalina predstavljaju nezavisan prediktor lošeg ishoda. Ovi nalazi podvlače činjenicu da kateholaminski odgovor, iako inicijalno adaptivan, postaje marker težine patofiziološkog poremećaja i insuficijentne hemodinamske stabilizacije.

Uvođenje vazopresora u terapijski algoritam hemoragijskog šoka ostaje jedno od najkontroverznijih pitanja u urgentnoj medicini i traumatologiji. Kako pokazuju Voelckel (13) i Nesek Adam i saradnici (14), upotreba noradrenalina i vazopresina može biti klinički korisna u situacijama kada agresivna tečna resuscitacija i kontrolisano krvarenje ne dovode do održive hemodinamske stabilnosti. Noradrenalin, kao primarni alfa-adrenergički agonist, povećava vaskularni tonus i krvni pritisak, dok vazopresin deluje preko V1 receptora, obnavljajući vaskularni odgovor kod pacijenata sa kateholaminskom refraktornošću, što se često javlja u kasnijim fazama šoka. Međutim, oba leka nose rizik od pogoršanja mikroperfuzije usled perifernog i splahničnog vazospazma, posebno kada se primenjuju u visokim dozama ili pre adekvatne kontrole izvora krvarenja. Ova dilema – balansiranje koristi u makrocirkulaciji i potencijalne štete u mikrocirkulaciji – čini odluku o upotrebi vazopresora izrazito kompleksnom i zahtevom za individualizovan pristup.

Značajan doprinos razumevanju optimalnog tajminga primene noradrenalina dali su Gauss i saradnici (15), koji su analizom velike kohorte ispitanika pomoću propensity-score metodologije ustanovili da rana primena noradrenalina kod pacijenata sa teškim traumatskim hemoragijskim šokom može smanjiti bolnički mortalitet. Ovaj rezultat sugeriše da strategija ranog farmakološkog potpomaganja perfuzije, ukoliko je pažljivo titrirana i praćena – može biti korisna u specifično definisanim kliničkim kontekstima, posebno u situacijama kada postoji rizik od preopterećenja tečnostima ili kada se hipotenzija ne može držati pod kontrolom isključivo nadoknadom tečnosti. Ipak, uprkos ovim ohrabrujućim rezultatima, konsenzus o preciznim protokolima, uključujući optimalni trenutak primene, doziranje, ciljane parametre i kriterijume za smanjenje ili ukidanje terapije i dalje nedostaje, što zahteva dalja klinička istraživanja.

Insuficijencija kortikosteroida povezana sa kritičnom bolešću (engl. Critical Illness-Related Corticosteroid Insufficiency - CIRCI)

CIRCI predstavlja kompleksan i često potcenjen endokrini poremećaj koji se javlja kod kritično obolelih i traumatizovanih pacijenata. Prema Sobolewska i saradnicima (5), CIRCI nastaje usled poremećaja funkcionisanja hipotalamo-hipofizno-adrenalne (HPA) ose tokom sistemskog stresnog odgovora. U uslovima teške infekcije, sepse, politraume, masivnog operativnog stresa ili akutnog respiratornog distres sindroma, fiziološki stresni odgovor može biti nedovoljan ili neadekvatan, što dovodi do disbalansa između potrebe organizma za kortizolom i njegove stvarne dostupnosti.

Sobolewska i saradnici (5) ističu da disfunkcija može biti posledica više mehanizama: smanjenog lučenja kortikotropin-oslobađajućeg hormona (CRH) i adrenokortikotropnog hormona (ACTH), smanjene osetljivosti nadbubrežne žlezde, poremećaja u sintezi i metabolizmu kortizola, smanjenih koncentracija transportnih proteina (kortikosteroid-vezajući globulin – CBG i albumin) ili smanjene ekspresije i funkcionalnosti glukokortikoidnih receptora u perifernim tkivima. Ovaj poremećaj doprinosi razvoju tzv. „relativne adrenalne insuficijencije“, gde ukupni kortizol može biti normalan ili čak povišen, dok je biološki stresni odgovor neadekvatan. Posledično, hemodinamska stabilnost je narušena, inflamatorni

ral review articles and meta-analyses (4,6,11) have confirmed its prognostic potential in predicting the development of PTSD, as well as perioperative and post-traumatic outcomes, there are methodological limitations that affect the consistency of results, differences in sampling time, sample matrix, definitions of outcome and characteristics of population. Despite these variations, the overall literature consistently indicates that cortisol is one of the most reliable endocrine indicators of acute stress, with significant clinical potential in early risk stratification, monitoring the adaptive response and identifying patients with an increased likelihood of adverse outcomes, both physiological and psychological.

The summary of key endocrine biomarkers, their pathophysiological role and prognostic significance in severe trauma is shown in Table 1.

Catecholamines and therapeutic implications

Catecholamines, primarily adrenaline and noradrenaline, are key mediators of neuroendocrine adaptation to hemorrhagic shock, enabling short-term maintenance of perfusion of vital organs through an increase in heart rate, myocardial contractility and systemic vascular resistance. However, this compensatory response has a pronounced dual physiological nature: although initially protective, excessive and prolonged release of catecholamines is associated with worsening of tissue oxygenation, metabolic acidosis, and a proinflammatory response. *Suh* et al. (12) showed that elevated catecholamine concentrations in emergency surgical patients had a strong correlation with mortality, while elevated noradrenaline values were an independent predictor of poor outcome. These findings underline the fact that the catecholamine response, although initially adaptive, becomes a marker of the severity of pathophysiological disorder and insufficient hemodynamic stabilization.

The introduction of vasopressors into the therapeutic algorithm of hemorrhagic shock remains one of the most controversial issues in emergency medicine and traumatology. According to *Voelckel* (13) and *Nesek Adam* et al. (14), the use of noradrenaline and vasopressin can be clinically useful in situations where aggressive fluid resuscitation and controlled bleeding do not lead to sustainable hemodynamic stability. Noradrenaline, as a primary alpha-adrenergic agonist, increases vascular tone and blood pressure, while vasopressin acts through V1 receptor, restoring the vascular response in patients with catecholamine refractoriness, which often occurs in the later stages of shock. However, both drugs carry the risk of worsening of microperfusion due to peripheral and splanchnic vasospasm, especially when they are administered in high doses or before the adequate control of the bleeding source. This dilemma – balancing the benefits in microcirculation and potential harm in microcirculation – makes the decision to use vasopressors extremely complex and requires an individualized approach.

A significant contribution to the understanding of optimal timing of administration of noradrenaline was made by *Gauss* and associates (15), who analyzed a great cohort of participants using the propensity-score methodology and found that that the early administration of noradrenaline in patients with severe traumatic hemorrhagic shock could reduce hospital mortality. This result suggests that the strategy of early pharmacologic perfusion support, if titrated and monitored carefully, may be useful in specifically defined clinical contexts, especially in situations when there is a risk of fluid overload or when hypotension cannot be controlled by fluid replacement alone. However, despite these encouraging results, consensus on precise protocols, including optimal timing of administration, dosing, target parameters, and criteria for reducing or withdrawing therapy, is still lacking, which requires further clinical research.

Critical Illness-related Corticosteroid Insufficiency – CIRCI

CIRCI is a complex and often underestimated endocrine disorder that occurs in critically ill and traumatized patients. According to *Sobolewska* and associates (5), CIRCI occurs due to the dysfunction of the Hypothalamic-Pituitary-Adrenal (HPA) axis activation during the systemic stress response. In conditions of severe infection, sepsis, polytrauma, massive surgical stress or acute respiratory distress syndrome, the physiological stress response may be insufficient or inadequate, leading to the imbalance between the body's need for cortisol and its actual availability.

Sobolewska et al. (5) point out that this dysfunction can be the result of several mechanisms: reduced secretion of corticotrophin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH), reduced sensitivity of the adrenal gland, disturbances in the synthesis and metabolism of cortisol, reduced concentrations of transport proteins (corticosteroid-binding globulin – CBG and albumin) or the reduced expression and functionality of glucocorticoid receptors in peripheral tissues. This disorder contri-

odgovor je disbalansiran, a organizam gubi mogućnost da održi homeostazu.

Klinički značaj CIRCI je izuzetno visok. Sobolewska i saradnici (5) navode da se stanje najčešće manifestuje refraktarnom hipotenzijom, lošim odgovorom na vazopresore, metaboličkim poremećajima (hiponatremija, hipoglikemija) i progresivnom organskom disfunkcijom. Uprkos savremenim dijagnostičkim pristupima, CIRCI često ostaje neprepoznat zbog svoje heterogene kliničke slike i nedostatka standardizovanih dijagnostičkih kriterijuma. Ovi pacijenti mogu imati produžen tok lečenja na jedinici intenzivne nege, sporiju stabilizaciju, veću stopu komplikacija i povećan mortalitet.

Posebno značajan doprinos daje rad Morabito i saradnika (16), koji naglašava da CIRCI nije ograničen samo na odrasle pacijente. Kod pedijatrijske populacije CIRCI predstavlja dodatni dijagnostički i terapijski izazov. Morabito i kolege (16) ukazuju na to da se kod dece odgovori HPA-ose na stres razlikuju u odnosu na odrasle, a referentne vrednosti, reaktivnost kortizola i testovi stimulacije još uvek nisu jasno definisani. Stoga, CIRCI u pedijatriji može biti još teže prepoznat, a posledice kašnjenja u dijagnostici mogu biti teže, naročito kod septičkih stanja i multiorganske disfunkcije. Kod dece se takođe ističe da varijabilnost u nivou kortizola zavisi od uzrasta, pubertetskog statusa, prethodne terapije glukokortikoidima i etilogije kritične bolesti.

Oba rada (5,16) naglašavaju da dijagnostički testovi uključujući adrenokortikotropnog hormonskog (ACTH) stimulacionog testa, imaju ograničenu pouzdanost u kritičnim stanjima. Promenjena koncentracija transportnih proteina, varijabilan metabolizam kortizola i fluktuacije stresnog odgovora dovode do poteškoća u tumačenju ukupnog kortizola. Sobolewska i saradnici (5) ukazuju na to da se sve više govori o važnosti slobodnog kortizola (engl. free cortisol) i alternativnih biomarkera, ali da još uvek nema jedinstvene preporuke koja bi precizno definisala kriterijume CIRCI. U pedijatriji je ovaj problem dodatno izražen zbog nedostatka validiranih pragova i odsustva široko prihvaćenih smernica (16).

Terapijski, CIRCI predstavlja oblast kontinuiranih kontroverzi. Hidrokortizon u niskim dozama predstavlja najčešće korišćenu terapijsku opciju, posebno kod pacijenata sa septičkim šokom refraktarnim na vazopresore. Sobolewska i saradnici (5) ističu da primena glukokortikoida može poboljšati hemodinamsku stabilnost, skratiti trajanje šoka i smanjiti potrebu za vazopresorskom podrškom, ali da nema jedinstvenog dokaza da terapija smanjuje ukupni mortalitet. U pedijatriji, Morabito i saradnici (16) posebno naglašavaju potrebu oprezne, individualizovane primene terapije, budući da dugoročni efekti steroidne terapije na HPA osu dece nisu dovoljnom istraženi i da postoji značajan rizik od supresije endogenog lučenja hormona.

Zajednički zaključak oba rada (5,16) jeste da CIRCI predstavlja složen, multifaktorski poremećaj koji ima veliki uticaj na ishod kritičnih stanja, ali da dijagnostički i terapijski pristupi ostaju nedovoljno standardizovani. Prepoznavanje ovog entiteta, pravovremena klinička procena i adekvatna terapijska intervencija od ključne su važnosti, budući da pravilno upravljanje CIRCI može poboljšati hemodinamsku stabilnost, smanjiti komplikacije i doprineti boljem preživljavanju kod kritično obolelih pacijenata.

Tireoidne promene i ne-tiroidni sindrom bolesti

Ne-tireoidni sindrom bolesti (NTIS) predstavlja specifičan endokrini odgovor na akutnu kritičnu bolest, traumu ili sistemsku inflamaciju i obuhvata niz biokemijskih poremećaja u osi hipotalamus–hipofiza–štitasta žlezda, najčešće izraženih kroz spuštene nivoe trijodtironina (T3), povišene vrednosti reverznog T3 (rT3) i relativno normalne ili smanjene koncentracije tiroksina (T4), uz odsustvo primarnog poremećaja štitaste žlezde. Prevalencija NTIS-a među kritično bolesnima izuzetno je visoka, a prema savremenim sistematskim pregledima i meta-analizama (17-19) sindrom nosi jasne prognostičke implikacije, potvrđujući svoju ulogu markera težine bolesti i potencijalnog modulatora patofiziološkog toka kritičnih stanja.

Meta-analiza Vidarta i saradnika (17) ističe da su sniženi T3 i poremećaji konverzije T4 u T3 snažno povezani sa mortalitetom, produženim boravkom u intenzivnoj nezi i većim rizikom od razvoja multiorganske disfunkcije. Ovaj rad obuhvatio je veliki broj heterogenih kohorti odraslih kritično bolesnih pacijenata i zaključio da NTIS nije samo epifenomen teške bolesti, već da predstavlja robustan i nezavisan prediktor lošeg ishoda. Rezultati upućuju na to da je intenzitet hormonske disfunkcije proporcionalan težini kliničkog stanja i stepenu sistemskog inflamatornog odgovora.

Studija Elmas i Kizilarslanoglua (18) dodatno proširuje klinički značaj NTIS-a, demonstrirajući da pacijenti sa ovim sindromom imaju značajno veći rizik od neuspeha neuspjeha neinvazivne ventilacije (NIV), što implicira da hormonalni status utiče na respiratornu rezervu, odgovor na terapijski pritisak

butes to the development of the so-called "relative adrenal insufficiency", where total cortisol may be normal or even elevated, while the biological stress response is inadequate. Consequently, hemodynamic stability is impaired, the inflammatory response is imbalanced, while the organism loses the ability to maintain homeostasis.

The clinical significance of CIRCI is extremely high. *Sobolewska* et al. (5) claim that the condition is most often manifested by refractory hypotension, poor response to vasopressors, metabolic disorders (hyponatremia, hypoglycemia) and progressive organ dysfunction. Despite modern diagnostic approaches, CIRCI often remains unrecognized due to its heterogeneous clinical picture and lack of standardized diagnostic criteria. These patients may have a prolonged course of treatment in the intensive care unit, slower stabilization, higher rate of complications and increased mortality.

A particularly significant contribution is made by the work of *Morabito* et al. (16), who emphasize that CIRCI is not limited only to adult patients. In the pediatric population, CIRCI is an additional diagnostic and therapeutic challenge. Morabito and associates (16) indicate that responses of HPA axis to stress are different in children in comparison to adults, while reference values, cortisol reactivity and stimulation tests are still not clearly defined. Therefore, CIRCI in pediatrics can be even more difficult to recognize in conditions of sepsis and multiple organ dysfunction. In children, it has also been noted that the variability in the cortisol level depends on age, pubertal status, previous glucocorticoid therapy and the etiology of the critical illness.

Both studies (5,16) emphasize that diagnostic tests including the adrenocorticotropic hormone (ACTH) stimulation test have the limited reliability in critical conditions. The altered concentration of transport proteins, variable cortisol metabolism, and fluctuations in the stress response lead to difficulties in interpreting total cortisol. *Sobolewska* et al. (5) point out the growing importance of free cortisol and alternative biomarkers, but that there is still no single recommendation that would precisely define the CIRCI criteria. In pediatrics, this problem is further expressed due to the lack of validated thresholds and the absence of widely accepted guidelines (16).

Therapeutically, CIRCI represents a field of continuing controversy. Low-dose hydrocortisone is the most commonly used therapeutic option, especially in patients with refractory septic shock. *Sobolewska* et al. (5) point out that the administration of glucocorticosteroids can improve the hemodynamic stability, shorten the duration of shock and reduce the need for vasopressor support, but that there is no unique evidence that the therapy reduces overall mortality. In pediatrics, *Morabito* et al. (16) particularly emphasize the need for careful, individualized administration of therapy, since the long-term effects of steroid therapy on the HPA axis of children have not been sufficiently examined and there is a significant risk of suppression of endogenous hormone secretion.

The common conclusion of both studies (5,16) is that CIRCI represents a complex, multifactorial problem that has a great impact on the outcome of critical conditions, but that diagnostic and therapeutic approaches remain insufficiently standardized. The recognition of this entity, timely clinical evaluation and adequate therapeutic intervention are of great importance because the proper management of CIRCI can improve hemodynamic stability, reduce complications and contribute to better survival in critically ill patients.

Thyroidal alterations and Non-Thyroidal Illness Syndrome

Non-Thyroidal Illness Syndrome (NTIS) is a specific endocrine response to an acute critical illness, trauma, or systemic inflammation and it includes a series of biochemical disorders in the Hypothalamic-Pituitary-Thyroid (HPT) Axis, most frequently expressed through lowered levels of triiodothyronine (T3), elevated levels of reverse T3 (rT3) and relatively normal or reduced concentrations of thyroxine (T4), with the absence of a primary thyroid disorder. The prevalence of NTIS among the critically ill is extremely high, and according to modern systematic reviews and meta-analyses (17-19), the syndrome has clear prognostic implications, confirming its role as a marker of disease severity and a potential modulator of the pathophysiological course of critical conditions.

It has been stated in the meta-analysis by *Vidart* et al. (17) that low T3 and T4-to-T3 conversion disorders are strongly associated with mortality, prolonged intensive care stay, and a higher risk of developing multiple organ dysfunction. This study included a large number of heterogeneous cohorts of adult critically ill patients and it was concluded that NTIS is not just an epiphenomenon of severe disease, but that it is a robust and independent predictor of poor outcome. The findings suggest that the intensity of hormonal dysfunction is proportional to the severity of clinical condition and degree

i celokupnu ventilatornu dinamiku. Autori su pokazali da su niske vrednosti T3 i poremećaji tiroksinske homeostaze povezani s ranijim prelaskom na invazivnu ventilaciju i povećavaju smrtnost, čime NTIS dobija ulogu prediktivnog biomarkera za stratifikaciju rizika kod respiratorno ugroženih bolesnika.

Širi patofiziološki okvir sindroma dodatno je razmatran u preglednom radu Sciacchitana i saradnika (9), koji su analizirali više meta-analiza i sistematskih pregleda kako bi procenili da li intervencije – uključujući hormonsku nadoknadu – mogu uticati na ishod NTIS-a. Autori zaključuju da, uprkos dobro dokumentovanom prognostičkom značaju NTIS-a, dokazi o terapijskoj koristi supstitucije T3 ili T4 ostaju nedovoljni i kontroverzni. Iako postoji teorijska racionalnost da hormonska korekcija može poboljšati metaboličku efikasnost i mitohondrijsku funkciju, ni jedna dosadašnja velika studija nije pružila dovoljno jakih dokaza da NTIS treba rutinski tretirati. Ovo dodatno potvrđuje shvatanje NTIS-a kao kompleksnog adaptivnog odgovora koji može biti koristan u ranoj fazi bolesti, ali maladaptivan u kasnijim stadijumima teškog kritičnog stanja.

U kontekstu imunoloških mehanizama, Wu i saradnici (20) pokazuju da NTIS utiče na imunofenotip i imunološku reaktivnost kod pacijenata sa teškim virusnim febrilnim sindromom praćenim trombocitopenijom. Posebno je istaknuto smanjenje T3 povezano sa modulacijom citokinske mreže, uključujući povećanu produkciju proinflamatornih citokina i izraženu limfocitnu disfunkciju. Ovaj rad sugeriše da NTIS ne predstavlja samo metabolički marker, već i da je aktivni aktivni učesnik u dinamici inflamacije, imunometabolizma i virusne patogeneze. Time se dodatno potvrđuje da su endokrini i imuni sistemi međusobno funkcionalno integrisani i da promene u hormonskim osama utiču na progresiju bolesti.

Specifičan doprinos fenotipu NTIS-a u traumatskim stanjima pruža studija Hifumija i saradnika (21), koja analizira promene tiroidnih hormona kod pacijenata sa teškom traumom koji zahtevaju masivnu transfuziju. Rezultati ukazuju da je kod ove populacije prisutna izražena supresija T3 i T4 zajedno sa povišenjem rT3, što korelira sa obimom tkivnog oštećenja, intenzitetom hemodinamske nestabilnosti i potrebom za agresivnim resuscitacionim merama. Autori zaključuju da se hormonske promene javljaju rano u toku trauma-šoka i predstavljaju validan indikator težine biološkog stresa i rizika od multiplih komplikacija.

Prema literaturi (17-21) NTIS predstavlja multidimenzionalni sindrom sa značajnim dijagnostičkim, prognostičkim i potencijalno terapijskim implikacijama. On je ujedno marker težine bolesti, odraz metaboličkog i imunološkog disbalansa i indikator povećanog rizika od respiratornog pogoršanja, hemodinamske nestabilnosti, multiorganske disfunkcije i mortaliteta. Razumevanje njegove patofiziologije, uloge u inflamaciji i uticaja na kliničke ishode od ključnog je značaja za optimalno upravljanje pacijentima u intenzivnoj nezi, osobito u kontekstima teške traume, sepsije i respiratorne insuficijencije.

Imunološki biomarkeri i predikcija ishoda

Inflamatorni biomarkeri, posebno interleukin-6 (IL-6) i C-reaktivni protein (CRP), predstavljaju centralne elemente u proceni rizika od razvoja sistemskog inflamatornog odgovora, sepse i multiple organske disfunkcije nakon teške traume. Njihova dinamika odražava intenzitet citokinske aktivacije, stepen tkivnog oštećenja i progresiju imunopatološkog odgovora.Dosadašnja istraživanja potvrđuju da su povišeni nivoi IL-6 i CRP-a u snažnoj korelaciji sa rizikom od razvoja rane i kasne multiorganske insuficijencije. Zbog toga su ovi biomarkeri nezaobilazni u početnoj, kao i u serijskoj kliničkoj proceni pacijenata (8).

U tom kontekstu, studija Durana i saradnika (7) donosi značajan doprinos razvoju personalizovanog pristupa u traumatologiji. Autori su, koristeći sveobuhvatnu analizu transkriptoma krvi, identifikovali specifične genske potpise koji se pojavljuju vrlo rano nakon povrede i dosledno predviđaju rizik od razvoja multiple organske disfunkcije (MODS). Ovaj prediktivni model zasnovan na molekularnom profilu omogućava ne samo ranu diferencijaciju pacijenata visokog rizika, već i precizno praćenje dinamike inflamacije i imunosupresije. Posebna vrednost studije leži u činjenici da transkriptomski biomarkeri mogu otkriti patofiziološka odstupanja pre nego što se ona manifestuju na klasičnim biohemijskim parametrima, što ih čini izuzetno pogodnim za naprednu stratifikaciju trauma populacije.

Pregled Trancă i saradnika (8) dodatno naglašava kompleksnost uloge inflamatornih biomarkera kod politraumatizovanih pacijenata. Autori zaključuju da se nakon teške traume razvija dvostruka imunološka disfunkcija: hiperinflamatorna faza (poznata kao SIRS), koju prati kompenzatorni antiinflamatorni odgovor (CARS). U tom procesu, biomarkeri poput IL-6, CRP-a, presepsina i prokalcitonina predstavljaju ključne alate za praćenje ove dinamike. Istaknuto je da je IL-6 najosetljiviji rani marker teškog SIRS-a, dok povišeni CRP u kasnijim fazama

of systemic inflammatory response.

A study by *Elmas and Kizilarslanoglu* (18) further expands the clinical significance of NTIS, demonstrating that patients with this syndrome have a significantly higher risk of noninvasive ventilation (NIV) failure implying that hormonal status affects respiratory reserve, therapeutic pressure response, and overall ventilator dynamics. The authors showed that low T3 levels and disorders of thyroxine homeostasis are associated with an earlier transition to invasive ventilation and that they increase mortality, thus giving NTIS the role of a predictive biomarker for risk stratification in respiratory compromised patients.

The wider pathophysiological framework of this syndrome was additionally discussed in a review by *Sciacchitano* et al. (9), who analyzed several meta-analyses and systematic reviews in order to assess whether interventions – including hormone replacement – might influence the outcome of NTIS. The authors conclude that, despite the well-documented prognostic significance of NTIS, the evidence of the therapeutic benefit of T3 or T4 substitution remains insufficient and controversial. Although there is a theoretical rationality that hormonal correction may improve metabolic efficiency and mitochondrial function, there is no large study to this day that has provided sufficiently strong evidence that NTIS should be routinely treated. This is further supported by the fact that NTIS is understood as a complex adaptive response that may be beneficial in the early stages of the disease, but maladaptive in the later stages of a severe critical condition.

In the context of immunological mechanisms, *Wu* et al. (20) have shown that NTIS affects the immunophenotype and immune reactivity in patients with severe viral febrile syndrome accompanied by thrombocytopenia. In particular, the reduction in T3 is associated with the modulation of cytokine network, including the increased production of pro-inflammatory cytokines and pronounced lymphocyte dysfunction. This study indicates that NTIS is not only a metabolic marker, but also an active participant in the dynamics of inflammation, immunometabolism and viral pathogenesis. This further confirms that endocrine and immune systems are functionally correlated and that alterations in hormonal axes affect the progression of disease.

A specific contribution to the phenotype of NTIS in traumatic conditions is provided by the study conducted by *Hifumi* et al. (21), who analyze the alterations of thyroid hormones in patients with severe trauma that require massive transfusion. The findings suggest that in this population there is a pronounced suppression of T3 and T4 together with an increase in rT3, which correlates with the extent of tissue damage, the intensity of hemodynamic instability and the need for aggressive resuscitation measures. The authors conclude that hormonal changes occur early in the course of trauma-shock and are a valid indicator of the severity of biological stress and the risk of multiple complications.

According to the literature (17-21), NTIS is a multidimensional syndrome with significant diagnostic, prognostic and potentially therapeutic implications. It is also a marker of disease severity, a reflection of metabolic and immune imbalance and an indicator of increased risk of respiratory deterioration, hemodynamic instability, multiple organ dysfunction and mortality. Understanding its pathophysiology, its role in inflammation, and impact on clinical outcomes is of great importance for the optimal management of patients in intensive care, especially in the context of severe trauma, sepsis and respiratory failure.

Immunological biomarkers and prediction of outcomes

Inflammatory biomarkers, especially interleukin-6 (IL-6) and C-reactive protein (CRP), are central elements in assessing the risk of developing a systemic inflammatory response, sepsis and multiple organ dysfunctions after severe trauma. Their dynamics reflect the intensity of cytokine activation, the degree of tissue damage and the progression of the immunopathological response. Previous research confirms that elevated levels of Il-6 and CRP are strongly correlated with the risk of developing early and late multiple organ failure. Therefore, these biomarkers are indispensable in the initial, as well as in the serial clinical assessment of patients (8).

In this context, the study by *Duran* et al. (7) makes a significant contribution to the development of a personalized approach in traumatology. The authors, using a comprehensive blood transcriptome analysis, identified specific gene signatures that appear very early after injury and consistently predict the risk of developing multiple organ dysfunction (MODS). This predictive model based on a molecular profile allows not only the early differentiation of high-risk patients, but also the precise monitoring of the dynamics of inflammation and immunosupression. The special value of the study lies in the fact that transcriptomic biomarkers can detect pathophysiological deviations before they

reflektuje održavanje inflamatornog stanja i rizik od sekundarne sepse. Analiza pokazuje da se pouzdana klinička odluka ne može doneti na osnovu samo jednog markera, već je neophodan integrisani pristup.

U specifičnom kontekstu neurotraume, Marta i saradnici (9) identifikuju dodatne prediktore mortaliteta kod pacijenata sa teškim traumatskim povredama mozga. Studija pokazuje da inflamatorni biomarkeri, zajedno sa fiziološkim parametrima i neurološkim skorovima, značajno unapređuju procenu prognoze. IL-6 se ističe kao marker povezan sa intrakranijalnom hipertenzijom, cerebralnom ishemijom i povećanim rizikom od ranih neuroloških komplikacija. Autori navode da integracija biomarkera sa postojećim prognostičkim modelima (npr. International Mission for Prognosis and Analysis of Clinical Trials in TBI – IMPACT, Corticosteroid Randomisation After Significant Head Injury – CRASH) može poboljšati prediktivnu tačnost, posebno u populaciji s ekstremno teškim povredama.

Pored inflamatornih markera, sve je više dokaza da demografske i biološke varijable doprinose razlikama u ishodima nakon teške traume. Brauckmann i saradnici (1) sproveli su obimnu epidemiološku analizu u politraumi i utvrdili jasne razlike u mortalitetu, komplikacijama i oporavku u odnosu na pol. Prema njihovim nalazima, žene reproduktivnog doba imaju povoljniju prognozu, što autori pripisuju zaštitnom efektu estrogena, boljim antiinflamatornim mehanizmima i povoljnijoj hemostatskoj regulaciji. Nasuprot tome, muškarci imaju veću incidenciju komplikacija, izraženiju inflamatornu reaktivnost i viši rizik od MODS-a. Ovi podaci sugerišu da razlike po polu predstavljaju važne biološke determinante koje bi trebalo uzeti u obzir u kliničkoj proceni.

Drugi značajan prediktorski parametar pomenut u literaturi odnosi se na metabolički odgovor na stres, posebno glikemiju pri prijemu u bolnicu. Armanious i saradnici (22) pokazali su da nivo glukoze ≥15 mmol/L predstavlja snažan i nezavisan prediktor mortaliteta kod politraumatizovanih pacijenata. Hiperglikemija u ranoj fazi traume odražava intenzitet neuroendokrinog stresa, oslobađanje kateholamina, povećanu hepatičnu glukoneogenezu i rezistenciju na insulin. Studija je pokazala da je povišena glikemija pri prijemu direktno povezana sa većom učestalošću septičkih komplikacija, prolongiranom ventilatornom podrškom i produženim boravkom u jedinici intenzivne nege. Ovaj parametar je jednostavan, dostupan i klinički veoma upotrebljiv, što ga čini važnim dodatkom sistemima rane procene.

Na osnovu svega, literaturni podaci (1,7-9,22) potvrđuju da je procena rizika kod pacijenata sa teškom traumom višeslojna i zahteva integraciju inflamatornih biomarkera, molekularnih signatura, metaboličkih parametara i bioloških varijabli. IL-6 i CRP ostaju osnovni indikatori inflamatorne aktivacije, dok transkriptomski modeli predstavljaju novu generaciju prediktivnih alata koji omogućavaju precizno prepoznavanje pacijenata sklonih komplikacijama. Polne razlike, kao i jednostavni metabolički parametri poput glikemije pri prijemu, doprinose dodatnoj diferencijaciji rizika i unapređuju personalizaciju tretmana u akutnoj traumatologiji. Najznačajniji imunološki i metabolički biomarkeri, njihova prognostička uloga i klinička primena sistematizovani su u Tabeli 2.

Komparacija prediktivnih biomarkera

Sveobuhvatna komparacija endokrinih, imunoloških, metaboličkih i demografskih biomarkera prikazana je u Tabeli 3. Integracija različitih endokrinih i imunoloških biomarkera omogućava detaljniju stratifikaciju rizika kod kritično obolelih i traumatizovanih pacijenata. Kortizol, kao klasičan indikator hormonskog stresa, pruža brzu informaciju o aktivaciji HHA-ose i adaptacionoj sposobnosti organizma, ali njegova prognostička vrednost može biti ograničena individualnom varijabilnošću i uticajem terapijskih intervencija. Kateholamini, pre svega noradrenalin i adrenalin, predstavljaju rani marker hemodinamskog stresa i korelaciju sa mortalitetom, ali su njihovi nivoi podložni fluktuacijama u zavisnosti od primene vazopresora i resuscitacije tečnostima. CIRCI i NTIS, sa druge strane, reflektuju relativne insuficijencije endokrinih osa i metaboličku adaptaciju, pri čemu njihova identifikacija zahteva kombinaciju laboratorijskih analiza i kliničkih kriterijuma.

Inflamatorni biomarkeri, poput IL-6 i CRP, pružaju dodatnu dimenziju procene, oni odražavaju intenzitet sistemskog inflamatornog odgovora i rizik od MODS-a, dok transkriptomski profili omogućavaju predikciju komplikacija pre nego što klinički manifestni parametri postanu abnormalni. Analiza ovih markera ukazuje na to da nijedan pojedinačni pokazatelj nije dovoljan za precizno predviđanje ishoda. Najbolja strategija podrazumeva sveobuhvatan pristup koji kombinuje endokrine, imunološke i metaboličke parametre, uz uvažavanje demografskih i individualnih karakteristika pacijenta.

Sveobuhvatna analiza literature pokazuje da kombinacija kortizola, IL-6 i transkriptomskih markera može povećati prognostičku tačnost, dok kateholamini i glikemija pri prijemu služe kao dodatni indikatori akutne ozbiljnosti stanja.

manifest on classical biochemical parameters, which makes them extremely suitable for advanced stratification of the trauma population.

The review by *Tranca* and associates (8) further emphasizes the complexity of the role of inflammatory biomarkers in polytraumatized patients. The authors conclude that a dual immune dysfunction develops after severe trauma: a hyperinflammatory phase (known as SIRS), followed by a compensatory anti-inflammatory response (CARS). In this process, biomarkers, such as IL-6, CRP, presepsin and procalcitonin are key tools for monitoring these dynamics. It was pointed out that IL-6 is the most sensitive early marker of severe SIRS, while elevated CRP in the later stages reflects the maintenance of the inflammatory state and the risk of secondary sepsis. The analysis shows that a reliable clinical decision cannot be made on the basis of only one marker, but an integrated approach is necessary.

In the specific context of neurotrauma, *Marta* et al. (9) identify additional predictors of mortality in patients with severe traumatic brain injuries. The study shows that inflammatory biomarkers, together with physiological parameters and neurological scores, significantly improve prognosis assessment. IL-6 stands out as a marker that is associated with intracranial hypertension, cerebral ischemia and increased risk of early neurological complications. The authors state that the integration of biomarkers with existing prognostic models (International Mission for Prognosis and Analysis of Clinical Trials in TBI – IMPACT, Corticosteroid Randomization after Significant Head Injury – CRASH) can improve predictive accuracy, especially in the population with extremely severe injuries.

In addition to inflammatory markers, there is increasing evidence that demographic and biological variables contribute to differences in outcomes after severe trauma. *Brauckmann* et al. (1) conducted a comprehensive epidemiological analysis in polytrauma and found clear differences in mortality, complications and recovery in relation to gender. According to their findings, women of reproductive age have a more favorable prognosis, which the authors attribute to the protective effect of estrogen, better anti-inflammatory mechanisms and more favorable hemostatic regulation. In contrast, men have a higher incidence of complications, more pronounced inflammatory reactivity, and a higher risk of MODS. These data suggest that gender differences represent important biological determinants that should be considered in clinical evaluation.

Another significant predictor parameter mentioned in the literature relates to the metabolic response to stress, especially glycemia at admission to the hospital. *Armanius* et al. (22) showed that glucose levels ≥15 mmol/L is a strong and independent predictor of mortality in polytraumatized patients. Hyperglycemia in the early phase of trauma reflects the intensity of neuroendocrine stress, release of catecholamine, increased hepatic gluconeogenesis, and insulin resistance. The study showed that elevated glycemia at admission is directly associated with a higher frequency of septic complications, prolonged ventilator support and prolonged stay in the intensive care unit. This parameter is simple, accessible and clinically very usable, making it an important addition to the systems of early assessment.

Based on the literature data (1,7-9,22), it has been confirmed that the risk assessment in patients with severe trauma is multifaceted and requires the integration of inflammatory biomarkers, molecular signatures, metabolic parameters and biological variables. IL-6 and CRP remain the basic indicators of inflammatory activation, while transcriptomic models represent a new generation of tools that enable accurate recognition of patients prone to complications. Gender differences, as well as simple metabolic parameters, such as glycemia at admission, contribute to additional risk differentiation and improve the personalization of treatment in acute traumatology. The most important immunological and metabolic biomarkers, their prognostic role and clinical application are systematized in Table 2.

Comparison of predictive biomarkers

A comprehensive comparison of endocrine, immunological, metabolic and demographic biomarkers is shown in Table 3. The integration of different endocrine and immunological biomarkers enables more detailed risk stratification in critically ill and traumatized patients. Cortisol, as a classic indicator of hormonal stress, provides quick information on the HPA-Axis activation and the adaptive capacity of the organism, but its prognostic value can be limited by individual variability and the influence of therapeutic interventions. Catecholamines, first of all noradrenaline and adrenaline, represent an early marker of hemodynamic stress and correlate with mortality, but their levels are subject to fluctuations depending on the administration of vasopressors and fluid resuscitation. CIRCI and NTIS, on the other hand, reflect relative insufficiency of endocrine axes and metabolic adaptation, while their identification

Kliničke implikacije i buduće perspektive

Razumevanje složene interakcije između endokrinog, imunološkog i metaboličkog odgovora kod kritično obolelih ima direktan značaj za kliničku praksu. Rano prepoznavanje pacijenata sa disfunkcijom HHA-ose, CIRCI ili NTIS omogućava pravovremenu intervenciju, uključujući ciljanu primenu glukokortikoida, optimizaciju hemodinamske podrške i individualizovano praćenje inflamatornog odgovora. Povezivanje biomarkera sa kliničkim skorovima i hemodinamskim parametrima može unaprediti odluke o intenzitetu nadzora, tipu resuscitacije i eventualnoj farmakološkoj intervenciji.

Buduće perspektive uključuju razvoj integrisanih prediktivnih modela zasnovanih na veštačkoj inteligenciji i algoritmu mašinskog učenja (engl. machine learning algoritmima), koji bi kombinovali kliničke parametre, endokrine i inflamatorne biomarkere, genetske i transkriptomske profile, kao i demografske faktore. Takvi modeli imaju potencijal da unaprede personalizovanu medicinu u kritičnoj nezi, smanje broj komplikacija i optimizuju korišćenje resursa.

Buduća istraživanja treba da se fokusiraju na standardizaciju vremenskih intervala uzorkovanja, definisanje referentnih vrednosti i evaluaciju terapijskih intervencija za NTIS i CIRCI, kako bi se smanjile varijacije u interpretaciji i omogućila ujednačena primena u kliničkoj praksi. Perspektiva obuhvata i razvoj novih biomarkera, uključujući slobodni kortizol, kombinovane citokinske indekse i molekularne profile koji mogu predvideti individualnu adaptaciju i rizik od nepovoljnih ishoda već u ranim fazama kritične bolesti.

Sveobuhvatno, integracija prediktivnih biomarkera u rutinsku kliničku praksu obećava unapređenje stratifikacije rizika, razvoj personalizovanih terapijskih strategija i smanjenje mortaliteta i komplikacija kod kritično obolelih pacijenata.

Zaključak

Kritično oboleli i traumatizovani pacijenti pokazuju složen i dinamičan odgovor endokrinog, imunološkog i metaboličkog sistema, pri čemu kortizol, kateholamini, CIRCI, NTIS i inflamatorni biomarkeri igraju centralnu ulogu u reflektovanju težine stresa, adaptacionih sposobnosti i rizika od komplikacija. Rani hormonski i inflamatorni odgovori, uključujući koncentracije IL-6, CRP i nivo glikemije pri prijemu, zajedno sa transkriptomskim i genetičkim profilima, omogućavaju precizniju stratifikaciju pacijenata i identifikaciju onih sa povećanim rizikom od multiorganske disfunkcije, septičkih komplikacija i nepovoljnih neuroloških ishoda. Individualne razlike, uključujući pol, prethodne terapije i tip traume, dodatno naglašavaju potrebu za personalizovanim pristupom u praćenju i terapiji kritičnih stanja.

Integracija prediktivnih biomarkera u kliničku praksu otvara mogućnosti za unapređenje rane dijagnostike, optimizaciju perioperativne i intenzivističke strategije i ciljanu farmakološku intervenciju. Buduća istraživanja treba da se fokusiraju na standardizaciju dijagnostičkih protokola, evaluaciju terapijskih intervencija i razvoj inovativnih modela predikcije rizika zasnovanih na veštačkoj inteligenciji i kombinaciji molekularnih, imunoloških i kliničkih parametara. Takav multidimenzionalni pristup ima potencijal da unapredi personalizovanu medicinu, smanji komplikacije i mortalitet, te poveća efikasnost i bezbednost lečenja kritično obolelih pacijenata.

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requires a combination of laboratory analysis and clinical criteria.

Inflammatory biomarkers, such as IL-6 and CRP, provide the additional dimension of assessment, they reflect the intensity of systemic inflammatory response, and the risk of MODS, while transcriptomic profiles enable the prediction of complications before parameters that are reflected clinically become abnormal. The analysis of these markers indicates that no single indicator is sufficient to accurately predict the outcome. The best strategy involves a comprehensive approach that combines endocrine, immunological and metabolic parameters, while taking into account the patient's demographic and individual characteristics.

A comprehensive analysis of the literature shows that the combination of cortisol, IL-6 and transcriptomic markers can increase the prognostic accuracy, while catecholamines and glycemia at admission serve as additional indicators of acute severity of the condition.

Clinical implications and future perspectives

Understanding the complex interaction between endocrine, immune and metabolic responses in the critically ill patients has direct implications for clinical practice. The early recognition of patients with HPA- Axis dysfunction, CIRCI or NTIS allows for timely intervention, including targeted administration of glucocorticoids, optimization of hemodynamic support and individualized monitoring of inflammatory response. Integrating the biomarkers with clinical scores and hemodynamic parameters can improve decisions about intensity of monitoring, type of resuscitation and possible pharmacological intervention.

Future perspectives include the development of integrated predictive models based on artificial intelligence and machine learning algorithms, which would combine clinical parameters, endocrine and inflammatory biomarkers, genetic and transcriptomic profiles, as well as demographic factors. Such models have the potential to improve personalized medicine in intense care, reduce complications and optimize the use of resources.

Future research should focus on standardizing the time intervals of sampling, defining reference values and evaluating therapeutic interventions for the NTIS and CIRCI, in order to reduce variations in interpretation and enable uniform application in clinical practice. The perspective also includes the development of new biomarkers, including free cortisol, combined cytokine indices and molecular profiles that can predict individual adaptation and risk of adverse outcomes even in the early stages of critical illness.

Overall, the integration of predictive biomarkers into routine clinical practice promises to improve risk stratification, develop personalized therapeutic strategies and reduce mortality and complications in critically ill patients.

Conclusion

Critically ill and traumatized patients show a complex and dynamic response of endocrine, immune and metabolic systems, where cortisol, catecholamines, CIRCI, NTIS and inflammatory biomarkers play a central role in reflecting the severity of stress, adaptive abilities and risk of complications. Early hormonal and inflammatory responses, including the concentration of IL-6, CRP and the levels of glycemia at admission, along with transcriptomic and genetic profiles, enable more accurate stratification of patients and identification of those at increased risk of multiple organ dysfunction, septic complications and adverse neurological outcomes. Individual differences, including gender, previous therapies and type of trauma, further emphasize the need for a personalized approach in monitoring and treating critical conditions.

The integration of predictive biomarkers into clinical practice opens up the opportunities for improving early diagnosis, optimizing perioperative and intensive care strategies, and targeted pharmacological intervention. Future research should focus on the standardization of diagnostic protocols, evaluation of therapeutic interventions, and development of innovative risk prediction models based on artificial intelligence and combination of molecular, immunological and clinical parameters. Such a multidimensional approach has the potential to improve personalized medicine, reduce complications and mortality and increase the efficiency and safety of treatment of critically ill patients.

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Tabela 1. Endokrini biomarkeri i predikcija ishoda

Biomarker	Predikcija ishoda	Klinička primena	Reference
Kortizol	Mortalitet, komplikacije, PTSP	Procena težine stanja, praćenje terapijskog odgovora	1,2,7,10,15
Kateholamini	Mortalitet, hemoragijski šok	Rano upravljanje šokom, indikacija za vazopresore	4,5,14,16
CIRCI	Povećan mortalitet, komplikacije	Hormonalna supstitucija kod insuficijencije	6,12
NTIS	Neuspeeh ventilacije, produženi boravak, mortalitet	Praćenje tireoidnog statusa, modulacija imunološkog odgovora	3,8,9,11,17

Tabela 2. Imunološki biomarkeri i predikcija komplikacija

Biomarker	Predikcija ishoda	Klinička primena	Reference
IL-6, CRP	Sepsa, MODS (multiple organ dysfunction syndrome)	Rano prepoznavanje inflamatornih komplikacija	18,19,20
Transkriptom krvi	Post-trauma MODS/POF	Razvoj preciznih prediktivnih modela	18
Glikemija	Mortalitet kod politraumatskih pacijenata	Procena rizika pri prijemu	23
Polne razlike	Različit rizik od komplikacija i mortaliteta	Demografska stratifikacija	21

Tabela 3. Komparacija endokrinih i imunoloških biomarkera

Biomarker	Tip	Predikcija ishoda	Klinička primena	Reference
Kortizol	Endokrinološki	Mortalitet, PTSP, komplikacije	Praćenje kritično bolesnih	1,2,7,10,15
Kateholamini	Endokrinološki	Mortalitet, šok	Upravljanje šokom	4,5,14,16
CIRCI	Endokrinološki	Mortalitet, produžene komplikacije	Hormonalna supstitucija	6,12
NTIS	Endokrinološki	Ventilacija, mortalitet	Praćenje tireoidnog statusa	3,8,9,11,17
IL-6, CRP	Imunološki	Sepsa, MODS	Praćenje inflamatornog odgovora	18,19,20
Transkriptom krvi	Imunološki	MODS/POF	Razvoj prediktivnih modela	18
Glikemija	Metabolički	Mortalitet	Procena rizika pri prijemu	23
Polne razlike	Demografski faktor	Mortalitet i komplikacije	Stratifikacija populacije	21

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Table 1. Endocrine biomarkers and outcome prediction

Biomarker	Outcome Prediction	Clinical Application	References
Cortisol	Mortality, complications, PTSD	Severity assessment, monitoring therapeutic response	1,2,7,10,15
Catecholamines	Mortality, hemorrhagic shock	Early shock management, indication for vasopressors	4,5,14,16
CIRCI (Critical illness–related corticosteroid insufficiency)	Increased mortality, complications	Hormonal substitution in insufficiency	6,12
NTIS (Non-thyroidal illness syndrome)	Ventilation failure, prolonged stay, mortality	Monitoring thyroid status, modulation of immune response	3,8,9,11,17

Table 2. Immunological biomarkers and complication prediction

Biomarker	Outcome Prediction	Clinical Application	References
IL-6, CRP	Sepsis, MODS (multiple organ dysfunction syndrome)	Early recognition of inflammatory complications	18,19,20
Blood transcriptome	Post-trauma MODS/POF	Development of precise predictive models	18
Glycemia	Mortality in polytrauma patients	Risk assessment at admission	23
Sex differences	Differential risk of complications and mortality	Demographic stratification	21

Table 3. Comparison of endocrine and immunological biomarkers

Biomarker	Type	Outcome Prediction	Clinical Application	References
Cortisol	Endocrine	Mortality, PTSD, complications	Monitoring critically ill patients	1,2,7,10,15
Catecholamines	Endocrine	Mortality, shock	Shock management	4,5,14,16
CIRCI	Endocrine	Mortality, prolonged complications	Hormonal substitution	6,12
NTIS	Endocrine	Ventilation, mortality	Monitoring thyroid status	3,8,9,11,17
IL-6, CRP	Immunological	Sepsis, MODS	Monitoring inflammatory response	18,19,20
Blood transcriptome	Immunological	MODS/POF	Development of predictive models	18
Glycemia	Metabolic	Mortality	Risk assessment at admission	23
Sex differences	Demographic factor	Mortality and complications	Population stratification	21

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