INNOVARE JOURNAL OF MEDICAL SCIENCES

Vol 14, Issue 2, 2026

Online - 2321-4406
Print - 2614-5006

Review Article

THE ROLE OF ELECTROLYTES ABNORMALITIES IN DETERMINING PROGNOSIS AMONG CRITICALLY ILL INDIVIDUALS – A COMPREHENSIVE REVIEW

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Received: 12 December 2025, Revised and Accepted: 19 February 2026

ABSTRACT

Electrolyte imbalance is a critical concern in severely ill patients, particularly in patients with chronic renal impairment, sepsis, those on mechanical ventilation, or receiving agents such as diuretics and vasopressin. These conditions can significantly disrupt electrolyte homeostasis and increase the risk of life-threatening complications. Within the intensive care unit setting, disturbances in major electrolytes are among the most frequent metabolic abnormalities encountered and are closely linked to higher morbidity and mortality rates. Electrolyte derangements are not merely reflections of disease severity but can actively exacerbate renal dysfunction, cardiovascular instability, and poor clinical outcomes. Therefore, precise fluid and electrolyte management has become an essential element of individualized pharmacologic care in critical illness. Optimizing electrolyte therapy, ensuring appropriate selection and titration of intravenous fluids, monitoring for drug-induced electrolyte changes, and preventing iatrogenic complications. Acute kidney injury has been reported in patients with either high or low chloride concentrations and increased mortality, while dysnatremia, hypokalemia, and hypocalcemia also carry important prognostic implications. Use of balanced crystalloids can mitigate chloride load, but vigilant monitoring remains necessary to prevent overcorrection and secondary disturbances. In summary, electrolyte management requires an evidence-based and pharmacologically precise approach, with close interprofessional collaboration to safeguard patient outcomes in critical care environments.

Keywords: Electrolyte imbalance, Chronic renal failure, Sepsis, Diuretics, Vasopressors, Sodium, Potassium, Calcium, Chloride, Magnesium, Bicarbonate.

 DOI: http://dx.doi.org/10.22159/ijms.2026v14i2.58231. Journal homepage: https://innovareacademics.in/journals/index.php/ijms

INTRODUCTION

Electrolyte imbalance is a familiar and multifaceted problem in severely ill individuals, mainly in those with chronic kidney disease, sepsis, shock, patients on mechanical ventilation, and individuals receiving diuretics or vasopressin. These clinical conditions can interfere with the body's normal electrolyte regulation, leading to serious complications and contributing to higher mortality and morbidity rates in intensive care units (ICUs) [1,6]. Importance in critical care includes electrolyte abnormalities involving sodium, potassium, chloride, calcium, and phosphate, which occur in nearly 90% of ICU patients. These imbalances are strongly linked with the degree of illness and are known to produce negative clinical outcomes, including extended ICU hospitalization, cardiovascular instability, impaired renal function, and increased overall treatment costs [1,7].

Significant contributors to electrolyte imbalances include chronic renal impairment, mechanical ventilation, and medications such as diuretics and vasopressors [7,10]. Comorbid conditions such as heart failure (HF), liver dysfunction, and sepsis add further complexity to fluid and electrolyte regulation. Hence, frequent monitoring and individualized pharmacologic adjustments are crucial in managing these patients effectively [4,6].

Relevance to prognosis

Even slight deviations in electrolyte concentrations can worsen organ function and negatively influence patient outcomes. Therefore, accurate electrolyte control through careful fluid selection, dose adjustments, and continuous observation for medication-related effects is essential for enhancing prognosis in critically ill populations [6,7].

ECG CHANGES IN POTASSIUM AND CALCIUM ABNORMALITIES

Electrolyte imbalances of potassium and calcium cause characteristic ECG changes that reflect altered cardiac conduction and repolarization. In hyperkalemia, tall, peaked T waves appear first, followed by a lengthened PR interval, absence of P waves accompanied by a broad QRS complex, which may progress to a sine-wave pattern and cardiac arrest [7]. In hypokalemia, the ECG shows that T waves appear reversed, ST-segment depression, and prominent U waves, with a prolonged QU interval, which can lead to ventricular arrhythmias [1,6].

Calcium abnormalities mainly affect the QT interval: hypercalcemia shortens the QT interval due to faster ventricular repolarization, whereas hypocalcemia prolongs the QT interval because of delayed repolarization, predisposing to Torsades de pointes [1,7].

Electrolyte disturbances are prevalent in ICU patients and can significantly impact outcomes. Table 1 summarizes the etiologies, clinical features, and management strategies for major electrolyte abnormalities commonly encountered in critical care [1,3].

Mg^{2+}, PO_4^-, and $H_2CO_3^-$ may also worsen the patient's condition. Increased bicarbonates and metabolic alkalosis, decreased bicarbonate, diabetic ketoacidosis, lactic acidosis, kidney disease, and metabolic acidosis. Phosphate may cause muscle weakness, fatigue, and bone pain; calcification of soft tissue [1,6].

Recent large-scale investigations using electronic health record datasets such as MIMIC-III and the electronic ICU Collaborative Research Database have shown that electrolyte abnormalities function not only as indicators of disease severity but also as active contributors to adverse clinical outcomes, including renal impairment and cardiovascular

Table 1: Etiology, symptoms, and treatment for electrolyte imbalance [1,6,24,34]

S. No.	Electrolytes	Etiology	Symptoms	Treatment
1.	Na^+standard range: 135–145 mmol/L			
	Hypernatremia (>150 mEq/L)	Dehydration, hyperglycemia, certain medications such as lithium, rifampicin, IV solutions, mannitol, alcohol, and excessive water loss.	Altered mental status, mild confusion, lethargy, coma, rhabdomyolysis.	Water retention with/without loop diuretics.
	Hyponatremia (<130 mEq/L)	Vomiting, diarrhea, gastrointestinal losses, heart failure, liver cirrhosis, syndrome of inappropriate antidiuretic hormone secretion, and adrenal insufficiency. Drugs such as carbamazepine, chlorpropamide, non-steroidal anti-inflammatory drugs, captopril, lithium, and imipramine.	Nausea and vomiting, headache, fatigue, severe muscle cramps and seizures, coma, and respiratory arrest.	Hypertonic saline (3%)
2.	K^+standard range: 3.5–5.5 (mEq/L)			
	Hypokalemia (<3.5 mEq/L)	Vomiting, diarrhea, GI Fistulas, renal losses, endocrine disorder, drugs. Beta 2 agonist theophylline, insulin, chloroquine, caffeine, dextrose, loop diuretics, thiazides, metabolic acidosis, and salicylates.	Muscle weakness, paralysis, ileums.	Oral IV K^+
	Hyperkalemia (>5.5 mEq/L)	Rhabdomyolysis, chronic kidney disease, adrenal insufficiency, digitalis, beta 2 agonists, K^+sparing diuretics, fluorides, heparin, succinyl choline.	Angina pectoris, diarrhea, weakness, myalgia, cardiac arrest.	Glucose, insulin, infusion sodium bicarbonate, Ca^+Gluconate, hemodialysis exchange resin.
3.	Cl−standard range: 96–106 mmol/L			
	Hypochloremia (<95 or<98 mmol/L)	Vomiting, diarrhea, and diuretics	Muscle weakness, fatigue, respiratory acidosis, and metabolic alkalosis	Fluid replacement addressing underlying causes decreases chloride intake
	Hyperchloremia (<106 mmol/L or 110 mmol/L)	Dehydration, excessive chloride intake, or kidney disease	Metabolic acidosis, hyperchloremia, and potential kidney damage	Fluid replacement addressing the underlying cause decreases chloride intake.
4	Ca^+standard range: 8.5–10.5 mg/dL			
	Hypocalcemia (>8.5 mg/dL)	Glycosides, ethanol, phenytoin, secondary hyperparathyroidism, parathyroid hormone production, impaired Vitamin D production.	Parathesias	Ca^+gluconate IV (10% solution 1 amp. At time slowly)
	Hypercalcemia (>14 mg/dL)	Vitamin D intoxication, lymphomas, thiazides, and Paget's disease.	Muscle cramps, tingling, fatigue.	Calcitonin 4–8 IV/kg IM, loop diuretics, Pamidronale (60–90) mg IV Over 2–4 h bisphosphate zoledronic acid (4 mg IV).

instability [29,30]. Emerging evidence also demonstrates a distinct "U-shaped" association between serum electrolyte levels, particularly sodium and chloride, and ICU mortality, suggesting that even mild deviations on either side of the normal range pose significant risk [31-33]. This finding underscores the growing importance of precise and individualized electrolyte management [24,34].

Advances in machine learning have introduced predictive models capable of anticipating electrolyte disturbances before they fully develop, enabling earlier intervention and marking a new shift toward proactive critical care [46,47]. In addition, contemporary research is exploring the specific benefits and risks of newer vasopressin analogs and balanced crystalloids, supporting a movement toward evidence-based, personalized fluid and electrolyte therapy that has not been extensively addressed in earlier literature [26-28].

Further, recent studies emphasize the prevalence and clinical impact of mixed or overlapping electrolyte disorders, which occur frequently in real-world ICU populations but were underappreciated in previous reviews [39,40]. Overall, the novelty of the current review lies in the integration of modern data analytics, predictive approaches, and a refined understanding of how even subtle electrolyte disturbances can influence outcomes in critically ill patients [7,46,47].

Table 2 shows how the body compensates for acid-base disorders. It compares the direction of change in pH, bicarbonate (HCO_3^-), and partial pressure of arterial carbon dioxide ($PaCO_2$) and gives formulas or expected compensation ranges. Metabolic disorders, lungs compensate by changing $PaCO_2$. Respiratory disorders, the kidneys compensate by changing HCO_3^-. Chronic disturbances allow more complete renal adjustments compared with acute changes. The pattern of pH, HCO_3^-, and $PaCO_2$ alternations helps identify the underlying disorder and evaluate the adequacy of compensation [21-23].

A decrease in pH accompanied by an elevation in $PaCO_2$ is interpreted as respiratory acidosis, whereas an increase in pH with a reduction in $PaCO_2$ indicates respiratory alkalosis [23,35]. When the pH is low, and HCO_3^- levels are also decreased, it suggests metabolic acidosis, whereas an elevated pH together with increased bicarbonate levels is considered indicative of metabolic alkalosis [35,36].

It is advised that clinicians perform arterial blood gas analysis and serum electrolyte testing at the same time, enabling comparison of bicarbonate levels from both tests to ensure accuracy. The anion gap (AG) is subsequently calculated and adjusted to albumin level 4.50 g/dL if it falls outside the normal range. The raised AG metabolic acidosis is most often resulting from ketoacidosis, lactic acidosis, renal failure,

Table 2: Estimating the body's compensatory responses to basic acid-base imbalances and understanding the resulting patterns of physiological changes [21-23,35,36]

Disorder	Prediction of the compensation	Value interval		
		pH	HCO_3^-	$PaCO_2$
Metabolic disorder	$PaCO_2$ ⇩ 1.25 mmHg per Mmol/L ⇩ in (HCO_3^-) or $PaCO_2$ = (HCO_3^-)+15	Decrease	Decrease	Decrease
Metabolic alkalosis	$PaCO_2$ ⇧ 0.75 mmHg per Mmol/L ⇧ in (HCO_3^-) or $PaCO_2$ = (HCO_3^-)+15	Increase	Increase	Increase
Respiratory alkalosis		Increase	Decrease	Decrease
Acute	(HCO_3^-) ⇩ 0.2 mmol/L per mmHg ⇩ in $PaCO_2$			
Chronic	(HCO_3^-) 0.4 ⇩ mmol/L per mmHg ⇩ in $PaCO_2$			
Respiratory acidosis		Decrease	Increase	Increase
Acute	(HCO_3^-) ⇧ 0.2 mmol/L per mmHg ⇧ in $PaCO_2$			
Chronic	(HCO_3^-) ⇧ 0.2 mmol/L per mmHg ⇧ in $PaCO_2$			

$PaCO_2$: Partial pressure of arterial carbon dioxide, HCO_3^-: Bicarbonate

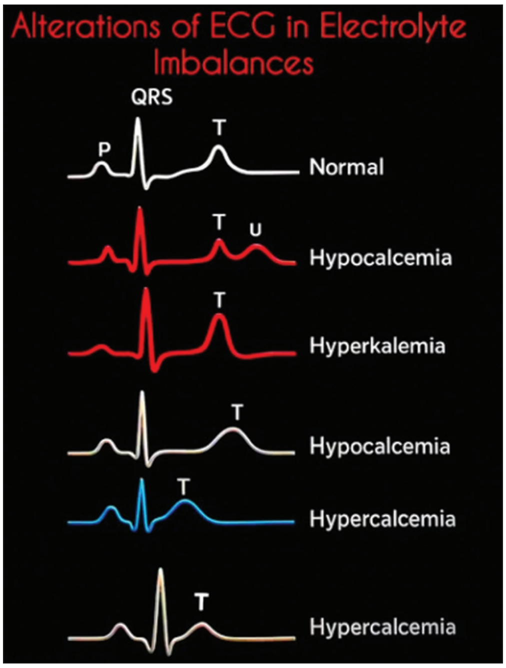

Fig. 1: ECG changes in potassium and calcium abnormalities [31-33]

or exposure to toxins. In contrast, normal or hyperchloremic metabolic acidosis generally occurs because of gastrointestinal bicarbonate loss or renal tubular acidosis. Accurate interpretation requires comparing changes in the AG with bicarbonate levels and assessing chloride variations in relation to sodium concentrations [35,36].

CHLORIDE AND FLUID COMPOSITION

Chloride, the major extracellular anion, is crucial for acid-base balance and renal perfusion but is often overlooked in clinical practice. Standard saline (0.9% NaCl) contains chloride concentrations (154 mmol/L) far above physiological levels, predisposing patients to hyperchloremic metabolic acidosis and renal vasoconstriction [24,34]. A pediatric before-and-after study compared outcomes before and after replacing saline with balanced fluids such as Plasmalyte and Lactated Ringer's. The switch reduced rates of hyperchloremia and hyperkalemia but slightly increased hypochloremia and hypokalemia. Importantly, no significant differences were found in acute kidney injury (AKI), suggesting that while balanced fluids improve biochemical profiles, their direct survival benefit remains uncertain [26,28]. In adults, hyperchloremia (≥110 mEq/L) has remained independently associated with increased AKI, multiple organ dysfunction, and ICU mortality. Conversely, hypochloremia also predicts poor outcomes in a large AKI cohort, where low chloride (<98 mEq/L) increased in-hospital and ICU mortality by roughly 40–50%. Together, these studies illustrate a U-shaped relationship among serum chloride and survival, emphasizing the importance of maintaining levels within the normal range [29,30,32].

SODIUM, POTASSIUM, AND CALCIUM IMBALANCES

Among cations, sodium shows the most well-defined prognostic pattern. Numerous studies demonstrate a U-shaped mortality curve, where both hyponatremia and hypernatremia increase death risk, though hyponatremia tends to be more dangerous [29,30]. In patients with respiratory failure, hyponatremia was associated with more than twofold higher mortality compared with normal sodium levels [29]. Similarly, hypokalemia and hypocalcemia are consistent markers of poor prognosis. Even mild reductions in potassium can trigger arrhythmias and neuromuscular dysfunction, whereas low calcium levels reflect systemic inflammation and critical illness severity [31-33]. Although magnesium abnormalities are common, their independent association with mortality is less consistent. These findings underline that maintaining electrolyte balance within physiological limits is vital, as deviation, whether hypo or hyper, can exacerbate multi-organ dysfunction [29,32].

Metabolic acidosis and respiratory alkalosis

- Pattern: More AG metabolic acidosis with $PaCO_2$ lower than expected
- ABG ex: Na 140, K 4.0, Cl 106, HCO 14, AG 20, $PaCO_2$ 24, 7.39 pH
- Mechanism: Metabolic acidosis is usually accompanied by compensatory hyperventilation, but if $PaCO_2$ is even lower than predicted, there is a concurrent respiratory alkalosis
- Clinical causes: Sepsis, salicylate toxicity, hepatic failure, or early shock (e.g., lactic acidosis in ICUs).

Metabolic acidosis and respiratory acidosis

- Pattern: More AG metabolic acidosis with $PaCO_2$ higher than expected
- ABG ex: Na 140, K 4.0, Cl 102, HCO 18, AG 20, $PaCO_2$ 38, 7.30 pH
- Mechanism: Respiratory acidosis (hypoventilation) prevents proper compensation for metabolic acidosis
- Clinical causes: Severe pneumonia, pulmonary edema, chronic obstructive pulmonary disease exacerbation with lactic acidosis.

Metabolic alkalosis and respiratory alkalosis

- Pattern: Both alkalotic components raise pH excessively; $PaCO_2$ does not rise as expected for metabolic alkalosis
- ABG ex: Na 140, K 4.0, Cl 91, HCO_3 33, AG 16, $PaCO_2$ 38, 7.55 pH
- Clinical causes: Hepatic disease, pregnancy, diuretic use, or early sepsis.

Metabolic alkalosis and respiratory acidosis

- Pattern: High HCO_3^- with elevated $PaCO_2$; pH often normal due to opposing effects
- ABG ex: Na 140, K 3.5, Cl 88, HCO_3 42, AG 10, $PaCO_2$ 67, 7.42 pH
- Clinical causes: chronic CO_2 retention combined with diuretic therapy (volume contraction alkalosis)

MIXED METABOLIC DISORDERS

Metabolic acidosis and metabolic alkalosis

- Pattern: Normal pH due to opposing processes; detected by discrepancy between AG and HCO_3^- changes

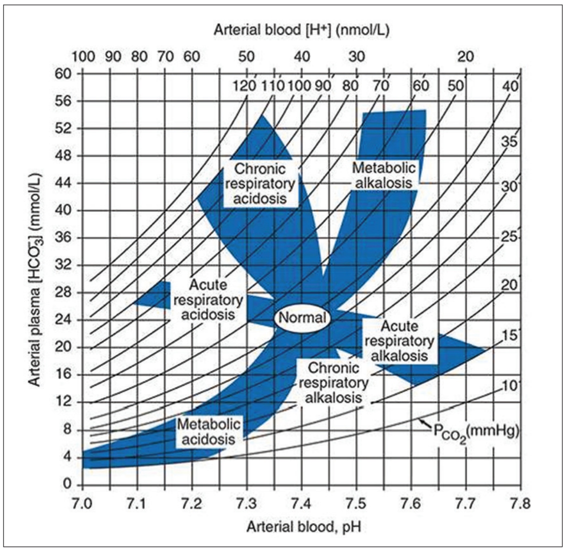

Fig. 2: Acid-base nomogram [21,22,35]

- ABG ex: Na 140, K 3.0, Cl 95, HCO_3 25, AG 20, $PaCO_2$ 40, 7.42 pH
- Clinical causes: Diabetic ketoacidosis treated with bicarbonate or renal failure with loss of gastric acid.

Metabolic acidosis and metabolic acidosis

- Pattern: Combined high AG and normal AG acidosis (HCO_3^- reduction from both AG rise and Cl^- increase)
- ABG ex: Na 130, K 3.5, Cl 110, HCO_3 10, AG 15, $PaCO_2$ 25, 7.20 pH
- Clinical causes: diarrhea along with lactic acidosis, toluene toxicity, or combined renal and metabolic acidosis (e.g., treated DKA) [21-23,35].

Electrolyte disorders in the ICU, recent multicenter analyses reveal that electrolyte abnormalities are nearly universal in ICU populations. In 2025, involving more than 2000 adult ICU patients, over 80% had at least one electrolyte disorder on admission, whereas nearly 40% presented with multiple concurrent disturbances hyperchloremia was the most common finding, affecting over half of all patients, followed by hyperkalemia and phosphate imbalances most patients developed new disorders during their ICU stay, highlighting the dynamic interplay among electrolytes and the importance of continuous monitoring. Intravenous correction was almost universal, but overcorrection occurred frequently, about 24% for hypokalemia and 9% for

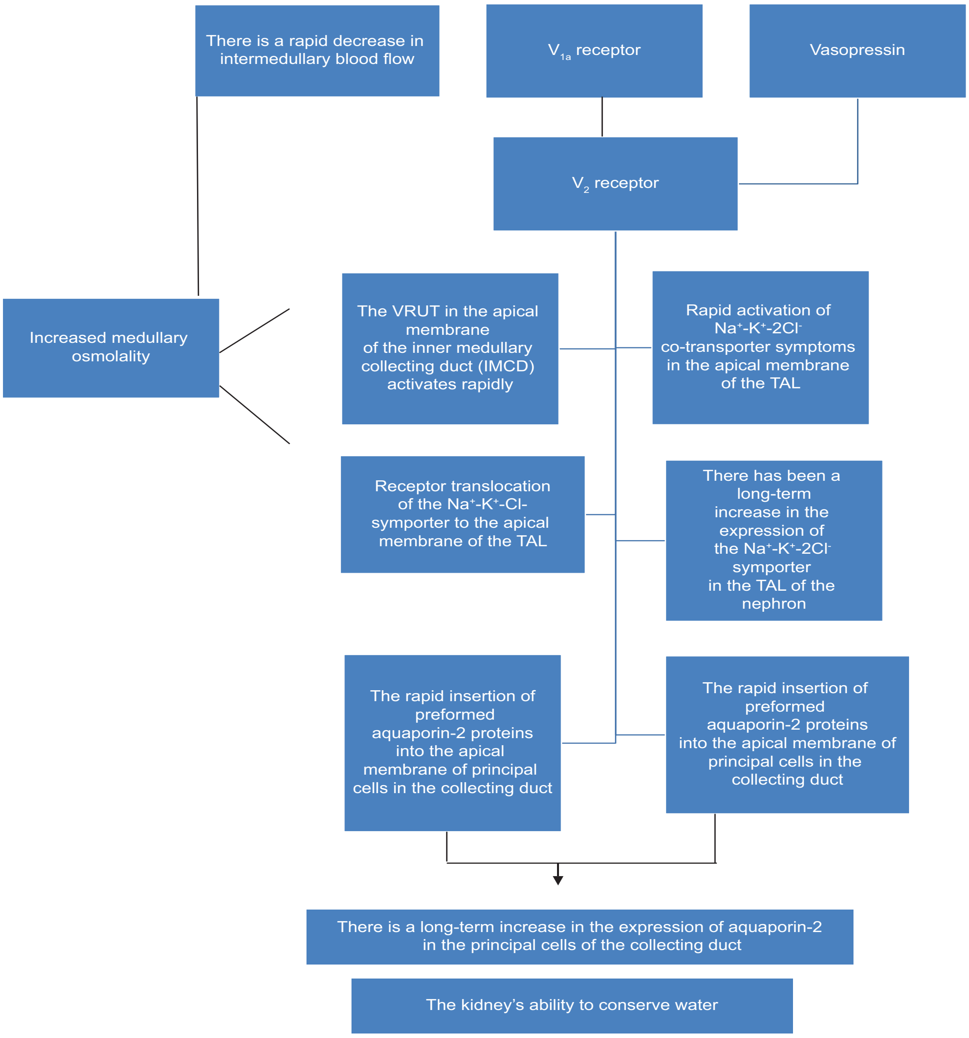

Fig 3: Vasopressin is understood to promote renal water conservation by acting on specific nephron segments. Its key effect is seen in the inner medullary collecting duct, where it substantially increases water reabsorption. It also activates vasopressin-regulated urea transporters in the inner medullary collecting duct, providing an additional mechanism for concentrating urine. In the TAL, vasopressin exerts a smaller, supporting influence on electrolyte and water regulation. Diagrams typically represent the dominant and minor pathways with thick and thin arrows, respectively, to highlight their relative contributions [52]

Table 3: The impact of diuretics on kidney excretion and renal blood flow dynamics [41,43,44]

	Cations							Anions			Uric		acid
	Na	**K**	**H**	**Ca**	**Mg**	**Cl**	**HCO_3**	**H_2PO_4**	**Acute**	**Chronic**	**RBF**	**CFR**	**FF**
Inhibitors of carbonic anhydrase	+	++	_	NC	V	(+)	++	++	1	_	_	_	NC
Osmotic diuretics	++	+	1	+	++	+	+	+	+	1	+	_	NC
Inhibitors of Na^+-K^+-2Cl−symport	++	++	+	++	++	++	2	2	+	_	V(+)	NC	V(−)
Inhibitors of the Na^+-Cl−symport	+	++	+	V(−)	V(+)	+	2	2	+	_	NC	V(−)	V(−)
Inhibitors of the renal epithelial sodium channels	+	_	_	_	_	+	(+)	NC	1	_	NC	NC	NC
Antagonists of mineral corticoid receptors	+	_	_	1	_	+	(+)	1	1	_	NC	NC	NC

Na: Sodium, K: Potassium, H: Hydrogen, Ca: Calcium, Mg: Magnesium, phosphate, Cl: Chloride, HCO_3: Bicarbonate, H_2PO_4: dihydrogen phosphate, RBF: Renal blood flow, CFR: Capillary filtration rate, FF: Filtration fraction

hypophosphatemia, indicating the need for individualized and cautious replacement protocols [38,39].

Except for uric acid, the described effects represent the immediate physiological responses produced by diuretics when significant volume depletion is not present, as such depletion would otherwise trigger complex compensatory mechanisms. For both cations and anions, these symbols denote absolute changes in fractional excretion, along with modifications in renal blood flow, glomerular filtration rate, filtration fraction, tubuloglomerular feedback, titratable acid (H^+), and NH_4^+ excretion. These general responses are characteristic of agents that inhibit carbonic anhydrase, although certain symport inhibitors, including metolazone and bumetanide, also increase bicarbonate and phosphate excretion, representing notable exceptions [42,45].

CLINICAL IMPLICATIONS AND PREDICTIVE TOOL

Conventional ICU severity scoring systems, such as SOFA and APACHE II, continue to play a key role in predicting mortality, but they do not identify specific, correctable factors. Electrolyte abnormalities, in contrast, are modifiable and therefore represent actionable targets for intervention. Recent developments in artificial intelligence and machine learning have enhanced predictive capabilities. Models trained on early ICU data (first 24 h) have successfully forecasted the onset of hyperchloremia and related complications, achieving an AUC of about 0.76· such systems can alert clinicians before electrolyte derangements fully develop, allowing for preventive adjustments in fluid choice or dosing, potentially reducing the incidence of AKI and mortality [46,47].

Future directions in vasopressin analog development are centered on the design of non-peptide agonists and antagonists that target specific vasopressin receptor subtypes for diverse therapeutic purposes. V1a-selective antagonists are being investigated for their efficacy in managing dysmenorrhea and Raynaud's Syndrome. V1b-selective antagonists are the subject of research for their potential roles in treating stress-related conditions, such as anxiety disorders, depressive states, ACTH-driven tumors, and Cushing's syndrome. V2-selective antagonists, as well as combined V1a/V2 antagonists, are under study for use in clinical scenarios including HF, syndrome of inappropriate antidiuretic hormone secretion, cirrhosis, hyponatremia, cerebral edema, diabetic nephropathy, and glaucoma. Furthermore, ongoing research into V2-selective agonists is focused on their application in the management of central diabetes insipidus, nocturnal enuresis, nocturnal polyuria, and urinary incontinence· [48,49].

In critical care, vasopressin analogs such as terlipressin and selepressin are tested for septic shock to improve blood pressure when other drugs fail. However, large clinical trials have found that while these drugs improve circulation, they have not yet shown clear survival benefits, so better patient selection and dosing strategies are needed [49,50]. Scientists are also designing short-acting and receptor-biased analogs that provide precise blood pressure control with fewer side effects, such as ischemia or hyponatremia. Another exciting area is the use of vasopressin analogs beyond shock treatment. New agents such as fedovaptagon, which act on V2 receptors, are being tested for urinary disorders such as nocturia by promoting water reabsorption and bladder relaxation. Meanwhile, desmopressin (dDAVP) is being studied for its hemostatic effects in cancer patients to reduce surgical or tumor-related bleeding [48,49,51].

CONCLUSION

Electrolyte imbalances are not simply laboratory abnormalities; they are powerful indicators and potential drivers of critical illness outcomes. Both hyper- and hypochloremia correlate strongly with kidney injury and mortality, while dysnatremia, hypokalemia, and hypocalcemia carry additional prognostic weight. Balanced crystalloids help reduce excessive chloride exposure, but vigilant monitoring remains essential to avoid overcorrection or secondary imbalances [53]. The integration of real-time electrolyte surveillance with predictive clinical decision support can transform critical care from reactive to proactive, enabling timely, individualized interventions. Maintaining electrolyte stability, especially within physiological chloride and sodium ranges, should be regarded as a cornerstone of modern intensive care medicine [53,54].

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