ORIGINAL ARTICLE

Electrolyte balance in dengue viral infection: Exploring the "hidden reef"

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ABSTRACT

Background: Dengue fever is a common acute febrile illness worldwide, caused by the dengue virus and transmitted mainly by the female Aedes aegypti mosquito. This study aims to determine the Association between serum electrolyte abnormalities and disease severity in dengue virus infection.

Material and Methods: This comparative cross-sectional study was conducted at the Pathology Department, Combined Military Hospital Malir, Karachi, from July to December 2022. It included 519 hospitalized patients with confirmed dengue infection; patients with other febrile illnesses were excluded. Cases were classified as severe or non-severe dengue fever. Hyponatremia and hypokalemia were defined as serum sodium <135 mEq/L and potassium <3.5 mEq/L, respectively. Data were analyzed using SPSS v25, with $p \leq 0.05$ considered significant.

Results: Of 519 dengue patients, 28.3% (n = 147) had severe dengue fever. Hyponatremia was common (46.8%) and significantly more frequent in severe cases (56.5%; $p < 0.001$), while hypokalemia occurred in 19.3% and was also associated with severity ($p < 0.001$). Median serum sodium was significantly lower in severe disease (129 vs. 137 mEq/L; $p < 0.001$), whereas potassium showed no significant difference ($p = 0.077$). Severe dengue was significantly associated with male sex and older age ($p < 0.001$).

Conclusion: Hyponatremia, mostly mild, was the most common electrolyte disturbance and showed a strong association with dengue severity. Potassium abnormalities were common but did not differ significantly across severity groups. Age and gender were also significantly associated with disease severity.

Keywords: Dengue viral infection, Electrolyte balance, Exploring, Hidden reef

BACKGROUND

Dengue fever (DF), an acute febrile illness is among one of the most prevalent vector-borne diseases globally. DF is caused by the Dengue virus (DENV), a virus from the Flaviviridae family that is transmitted by female mosquito of the genus Aedes, mainly Aedes aegypti. Facilitating the spread of the virus, especially in densely populated and urbanized areas these vectors are prevalent in tropical and subtropical regions. Although the viral aetiology of DF has been recognized for many years, Dengue Viral infection (DEVI), also known as break-bone fever, remains largely uncontrolled worldwide resulting in significant human morbidity, mortality, and economic impact.[1] With an estimated 390 million infections occurring annually, DEVI has become endemic in over 100 countries, posing a substantial global burden, especially in Asia that bears the majority of the actual burden, accounting for 70%.[2] In recent decades the incidence of DEVI has grown dramatically around the world. Over the last two decades the number of dengue cases reported to WHO increased over 8-fold, from 505,430 cases in 2000to over 2.4 million in 2010and 5.2 million in 2019.[3]

Since 1994, Pakistan has been considered dengue-endemic, and the disease has become a public health problem since 2006, resulting in around 147,200 cases and over 800 deaths from 1995 to 2019.[4] Compared to the same period during the four previous years the number of reported dengue cases is significantly higher in 2022 (between January and September). Between 1st January and 27th September 2022, a total of 25,932 confirmed dengue cases and 62 deaths (CFR 0.25%) were reported in Pakistan, with 74% of these cases reported in September alone. The current surge in cases follows unprecedented flooding that began in mid-June 2022.[5]

The DEVI can present as asymptomatic (as many as 50% of individual infections), dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS), which is the most severe form of

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dengue infection.[6] The pathophysiology of dengue involves a complex interplay of viral replication, vascular permeability and various immune responses. Increased vascular permeability, a hallmark of severe dengue, can lead to fluid leakage, hemoconcentration, and electrolyte disturbances. Renal involvement in DEVI that can range from fluid & electrolyte imbalances to AKI associated with high morbidity and mortality is one of the least studied complications.[7] Electrolyte imbalances may potentially contribute to the development of complications such as cardiac arrhythmias, seizures, and muscle weakness in Dengue infected patients.[8] Hyponatremia, one of the electrolyte disorders that occurs in DF have been reported to heighten the risk of mortality in hospitalized patients while the DF patients with hypernatremia have been remained in intensive care for a more extended period with a higher risk of death.[9]

The relationship between electrolyte disturbances and disease progression in dengue infection also appears complex and is not entirely consistent across the studies.[10] Previous studies that investigated the prevalence of electrolyte disturbances in dengue fever, reported hyponatremia as a common finding in dengue patients.[11] However, the prevalence and clinical significance of other electrolyte abnormalities remained less well-defined.[12]

Given the potential clinical significance of electrolyte imbalances in dengue fever and the existing gaps in the literature, this study aimed to comprehensively evaluate the prevalence and patterns of serum electrolyte disturbances and their association with disease severity in a large cohort of patients suffering from DEVI. Our study findings provided valuable insights into the clinical management of dengue which may help in the development of targeted interventions to prevent and manage electrolyte abnormalities in these patients.

MATERIAL AND METHODS

This Comparative Cross sectional study was conducted at the Department of Pathology Combined Military Hospital Malir, Karachi Pakistan, from July-December, 2022 after obtaining ethical approval (79/2021/ Trg/EPS) from institute. Sample size was calculated using OPENEPI software version 3to estimate the prevalence of hyponatremia. Using an expected prevalence of 29.3%[9], a two-sided 95% confidence level and a margin of error of 5%, the sample size was estimated to be approximately 319 patients. We enrolled 519 patients. There were five hundred and nineteen patients with confirmed infection (either NS1, IgM or IgG positive with consistent symptoms) were included in the study utilizing a non-probability, consecutive sampling. Patients with chronic kidney disease, liver disease, any endocrine disorder affecting water and electrolyte balance, or suffering from any febrile illness other than DEVI were excluded from the study. This new classification was developed considering the level of clinical severity to establish management guidelines and to facilitate dengue reporting and surveillance.

Blood specimens from both groups were collected in Lithium Heparin tubes and sent to Pathology labor the evaluation of serum electrolyte levels. Serum sodium, potassium and chloride levels were estimated by Electrolyte Kit method using ion selective electrode (ISE) semi-auto analyser. Hyponatremia was defined as serum sodium levels less than 135 Meq/L while Hypokalemia was defined as Serum potassium levels less than 3.5 Meq/L. Samples were processed within 24 hours after collection. Electrolyte abnormalities were further graded as shown in Figure-I.

Lab results were entered and analysed using Statistical Package for Social Sciences version 25. Serum sodium (mEq/L) was categorized into five clinically relevant groups: severe hyponatremia (<121), moderate hyponatremia (121–130), mild hyponatremia (131–134), eunatremia (135–145), and hypernatremia (>145). Descriptive statistics were used to obtain median for continuous variables. Prevalence of electrolyte abnormalities was calculated using frequencies and percentages. Continuous variables, including serum sodium levels, serum potassium levels, and age, were calculated as median with interquartile range (IQR), as appropriate. Categorical variables were summarized as counts and percentages and compared using the Chi-square test. P-value of< 0.05 was considered statistically significant.

RESULTS

Among 519 laboratory-confirmed dengue patients, 147 (28.3%) had SDF, while 372 (71.7%) had NSDF. The mean age of patients was 44.4 ± 13.5 years, with a male predominance (n=395, 76.1%).The mean serum sodium level was 134.45 ± 6.73mEq/L, while the mean serum potassium level was 4.0 ± 0.6mEq/L. Overall, 243 out of 519 (46.8%) patients exhibited hyponatremia, with

mild hyponatremia being the most frequent abnormality (n=132, 25.4%).Based on categorical classification, hypokalemia was also observed in a substantial proportion of patients (n=100, 19.3%). Frequency distribution of various categories of electrolyte status across the severity of dengue diseases has been shown in(Figure-IIa &IIb).

Crosstabulation of categorical data showed a significant association between gender and dengue severity (χ^2 test, $p < 0.001$), with males more frequently represented among severe cases as compared to female patients (Table-I).

On continuous analysis, serum sodium levels were significantly lower in SDF compared to NSDF (Mann–Whitney U = 11,209.5, Z = –10.493, $p < 0.001$). The mean ranks indicated markedly lower sodium levels in SDF patients (150.26 vs. 303.37). Serum potassium levels were also comparable between two groups (mean rank 241.5 vs. 267.3), but the difference did not reach statistical significance (Mann–Whitney U = 24,624, Z = –1.768, p = 0.077) (Table-II).

Median age of patients with SDF was significantly higher compared to NSDF (Mann–Whitney U = 15,479.5, Z = –7.708, $p < 0.001$) (Table-II).

Table-I: Association of gender and electrolyte status with severity of dengue (n=519).

Variables		SDF (n=147)	Non-SDF (n=372)	Total (n=519)	p-value* (χ^2 test)
Gender	Male	96 (65.3%)	299 (80.4%)	395 (76.1%)	<0.001
	Female	51 (34.7%)	73 (19.6%)	124 (23.9%)	
Serum Na^+status	Normal Na^+ (135-145mEq/L)	32 (21.8%)	234 (62.9%)	266 (51.3%)	<0.001
	Mild Hyponatremia (131-134mEq/L)	30 (20.4%)	102 (27.4%)	132 (25.4%)	
	Moderate Hyponatremia (121-130mEq/L)	64 (43.5%)	21 (5.6%)	85 (16.4%)	
	Severe Hyponatremia (<121 mEq/L)	19 (12.9%)	7 (1.9%)	26 (5.0%)	
	Hypernatremia (>145mEq/L)	2 (1.4%)	8 (2.2%)	10 (1.9%)	
Serum K^+status	Normal K^+ (3.5 - 5.1mEq/L)	92 (62.6%)	314 (84.4%)	406 (78.2%)	<0.001
	Mild Hypokalemia (3.1-3.4mEq/L)	29 (19.7%)	48 (12.9%)	77 (14.8%)	
	Moderate Hypokalemia (2.5 - 3.0mEq/L)	10 (6.8%)	5 (1.3%)	15 (2.9%)	
	Severe hypokalemia (<2.5mEq/L)	5 (3.4%)	3 (0.8%)	8 (1.5%)	
	Hyperkalemia (>5.1mEq/L)	11 (7.5%)	2 (0.5%)	13 (2.5%)	

$p \leq 0.05$ considered as statistically significant

Table 2: Comparison of AGE, serum Na^+ levels and serum K^+ levels among SDF and NSDF patients (n=519).

Parameters	SDF (n=147)	NSDF (n=372)	*p*-value* (Mann Whitney U test)
Age (Years) Median (IQR)	54 (42-63)	41 (31-52)	<0.001
Serum Na^+ (mEq/L) Median (IQR)	129 (124-134)	137 (133-140)	<0.001
Serum K^+ (mEq/L) Median (IQR)	3.9 (3.4-4.4)	4.1 (3.6-4.4)	<0.077

*$p \leq 0.05$ considered as statistically significant

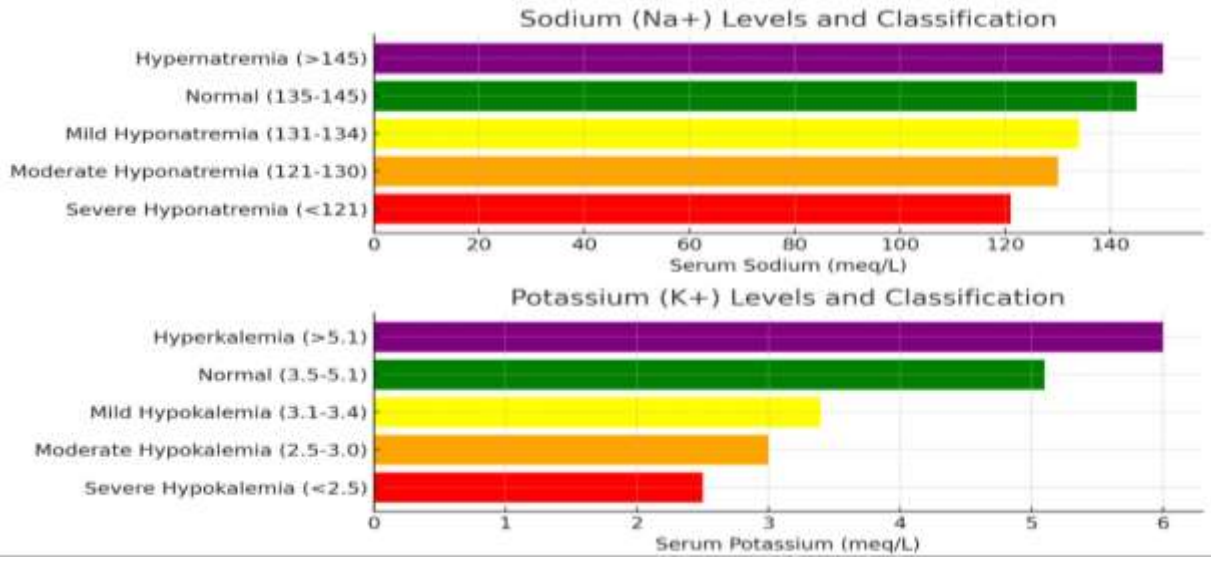

Figure-I: Electrolyte abnormalities.

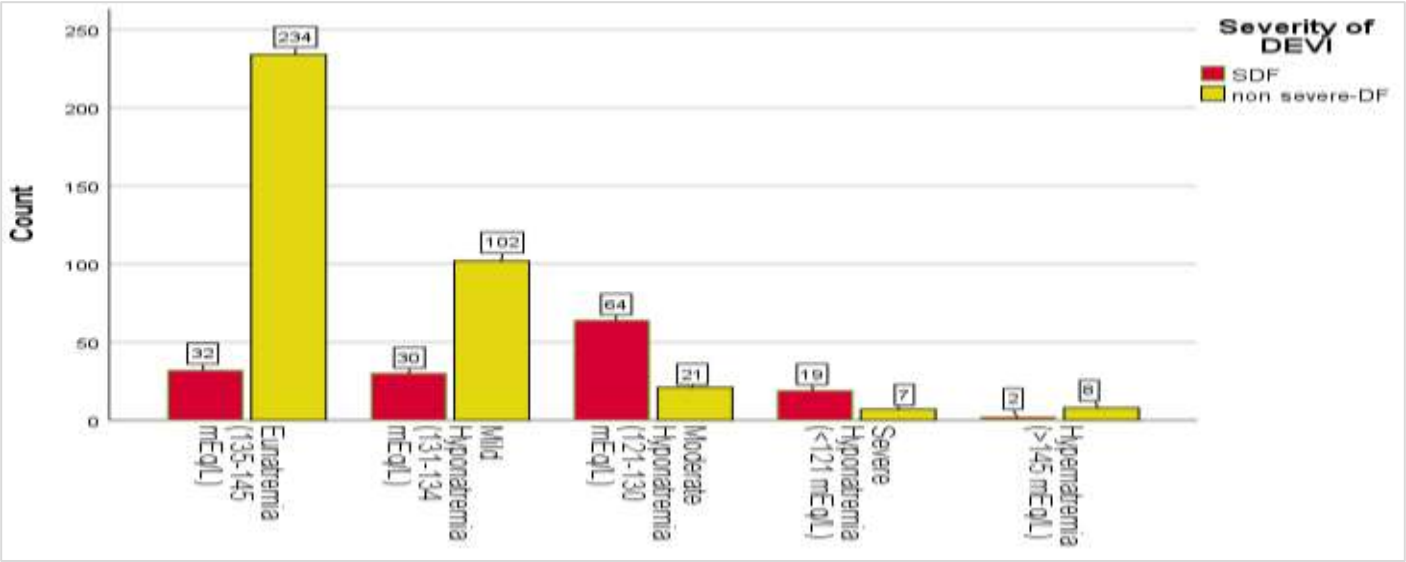

Figure-IIa: Categorised serum Na^+ status in Dengue patients.

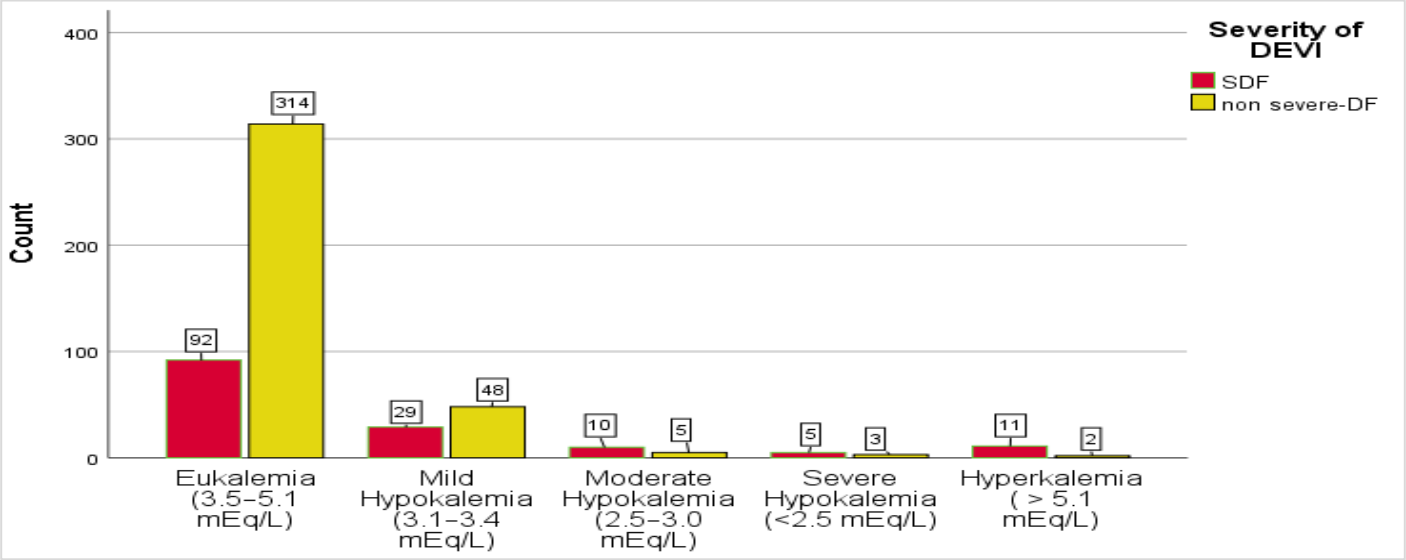

Figure-IIb: Categorised serum K^+ status in dengue patients.

DISCUSSION

The present study investigated the status and clinical significance of serum electrolytes in a large cohort of 519 adult patients with laboratory-confirmed dengue infection, categorised by disease severity. Our principal finding is the high prevalence of hyponatremia (46.8%) and its strong, statistically significant association with severe dengue fever (SDF). Patients with severe dengue had significantly lower median serum sodium values compared to non-severe dengue. Furthermore, while mean potassium levels did not significantly differ, a significant categorical association was observed between both hypo- and hyperkalemia and the severity of dengue ($p<0.001$). Our results showed that it is important to keep in observation of electrolytes especially sodium level, because it may possibly can cause early clue to more serious or complicated disease progression.[1] In our study patients, a total of 46.8% of cases showed hyponatremia (serum sodium below 135 mEq/L), a figure that falls well within the broad range previously reported in studies from India and Southeast Asia.[2,3] In other tertiary care settings sodium level matches as the average serum sodium level we observed was 134.45 ± 6.73 mEq/L.[4] We found that the sodium levels patients with severe dengue fever (SDF) had significantly lower than those with non-severe dengue fever (NSDF): the median sodium level was 129 mEq/L in SDF patients versus 137 mEq/L in NSDF patients ($p < 0.001$). This difference was much more when we looked at specific categories of hyponatremia. Six times more Moderate hyponatremia (sodium between 121–130 mEq/L) was seen in SDF patients (43.5%) than in

NSDF patients (5.6%). Similarly, severe hyponatremia (sodium below 121 mEq/L) was far more prevalent in the SDF group (12.9%) compared to the NSDF group (1.9%).[1]

SIADH is considered the most common cause of hyponatremia in dengue.[5] When the dengue virus sets off a strong inflammatory response along with the body's stress reaction and disturbances in fluid balance it can trigger the release of ADH even when it's not needed. In severe dengue, increased capillary permeability leads to significant plasma leakage from the vasculature a hallmark of the viral infection.[7] This extravasation reduces effective circulating volume, prompting the body to retain water, which in turn dilutes sodium concentrations in the bloodstream.[6] The resulting hyponatremia further stimulates the release of ADH, perpetuating the cycle of fluid retention and electrolyte imbalance.[7]

Emerging evidence from the region indicates a strong association between the severity of hyponatremia and the clinical severity of dengue, consistent with recent studies.[8] This contrasts with earlier reports that, while recognizing hyponatremia as a common laboratory finding in dengue, failed to establish a clear correlation with disease severity.[9] Notably, moderate to severe hyponatremia occurs significantly more frequently in patients diagnosed with SDF, a finding that should alert clinicians to its potential implications. Given that pronounced hyponatremia is linked to an elevated risk of neurological complications including encephalopathy and seizures its presence necessitates vigilant monitoring and heightened clinical awareness.[10]

In our cohort, hypokalemia defined as serum potassium <3.5 mEq/L was present in 19.3% of patients, a proportion notably lower than the 34% reported in a prior study from South India by Rajalekshmy and Vadivelan.[11] When comparing mean serum potassium levels between patients with SDF and those with NSDF, the values were comparable, and the difference did not achieve statistical significance, although it approached it ($p = 0.077$). However, when patients were stratified into potassium categories normal, hypokalemic (<3.5 mEq/L), or hyperkalemic (>5.0 mEq/L) a statistically significant association emerged between abnormal potassium levels and disease severity ($p < 0.001$). Both hypo- and hyperkalemia were markedly more prevalent in the SDF group. The development of hypokalemia in these patients is likely multifactorial, resulting from gastrointestinal losses due to vomiting or diarrhea, as well as direct viral effects on renal function. Dengue virus infection can induce subclinical renal tubular dysfunction, including non-anion gap (non-acidotic) renal tubular acidosis, even in the absence of overt kidney injury.[12] Although renal involvement in dengue is often mild or asymptomatic, it may occasionally progress to AKI or specific tubular damage, both of which can disrupt potassium homeostasis and contribute to electrolyte imbalances.[12]

The substantially higher prevalence of hyperkalemia 7.5% in patients with SDF versus only 0.5% in those with NSDF holds significant clinical implications.[13] Although hyperkalemia is relatively infrequent in dengue overall, its presence is often indicative of serious complications, including AKI, rhabdomyolysis, or severe metabolic acidosis, all of which are well-documented markers of severe dengue.[14] The marked increase in hyperkalemia among SDF patients underscores its value as a critical red flag, suggesting that even if less common than hyponatremia it may signal the onset of multi-organ dysfunction.[15]

In alignment with prior studies on dengue severity, patients in our SDF group were significantly older, with a median age of 54 years, compared to 41 years in the NSDF group.[16] Advanced age is a well-recognized risk factor for adverse outcomes in dengue infection.[17] When this older demographic profile coexists with significant electrolyte disturbances particularly moderate to severe hyponatremia and hyperkalemia, as observed in our cohort it signifies a markedly elevated clinical risk. This convergence underscores the necessity for vigilant monitoring and more aggressive supportive management. Although a recent study has suggested that electrolyte abnormalities at the time of hospital admission may not reliably predict length of stay or mortality[18], our findings offer a contrasting perspective. We demonstrate that the degree of electrolyte imbalance especially moderate to severe hyponatremia and the presence of hyperkalemia is closely tied to the pathophysiological processes driving severe dengue. The robust association between hyponatremia and SDF implies that it is not merely an incidental laboratory anomaly; rather, it likely reflects the profound systemic consequences of the disease, particularly the vascular leakage and neurohormonal dysregulation such as inappropriate ADH secretion that characterize critical dengue.[1,6,7]

CONCLUSION

Hyponatremia was the most common electrolyte abnormality, predominantly mild, and was strongly associated with dengue severity. Potassium abnormalities were also frequent, though the difference in mean levels between severity groups was not statistically significant. Both age and gender showed significant associations with dengue severity.

CONFLICT OF INTEREST

None

GRANT SUPPORT & FINANCIAL DISCLOSURE

Declared none

AUTHOR CONTRIBUTION

Aisha Ayyub: Substantial contribution conception, study design, acquisition of data, drafting of work, critical revisions, final approval, and accountable for all aspects of publication.

Shagufta Yousaf: Substantial contribution conception, critical review, final approval, accountable for all aspects of publication

Atif Ahmed Khan: Substantial contribution conception, analysis and interpretation of data, final approval, accountable for all aspects of publication

Sadia Dawood: Substantial contribution conception, analysis and interpretation of data, drafting of work, final approval, and accountable for all aspects of publication.

Sadia Babar, Aysha Khan: Substantial contribution to acquisition of data, reviewing manuscript for important intellectual content, final approval, and accountable for all aspects of publication

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