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ORIGINAL ARTICLE

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A comprehensive investigation into the ranges of laboratory tests present in cerebrospinal fluid across various types of meningitis within different age categories

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ABSTRACT

Background. Diagnosing meningitis requires a lumbar puncture to analyze cerebrospinal fluid (CSF) and determine the causative pathogen. Key diagnostic measures include Glucose and Protein concentrations, cell count, differential leukocyte count, Gram stain, culture, and PCR if necessary. **Objective.** Our analysis assessed patterns in key biomarkers—neutrophils, lymphocytes, cerebrospinal fluid white blood cell count, and CSF/blood Glucose and Protein ratios—across various types of meningitis, including meningococcemia, meningococcal, tuberculous, pneumococcal, aseptic, and other bacterial meningitis. We examined these biomarkers within distinct age categories: children (0-12 years), adults (13-64 years), and the elderly (≥ 65 years). **Methods.** Descriptive statistics were used to analyze various types of meningitis across different age groups. We assessed the normality of laboratory biomarkers using the Shapiro-Wilk test, and applied Welch ANOVA to explore potential differences in biomarker levels among various types of meningitis. A Games-Howell post hoc test was used to identify specific pairs of meningitis types with statistically significant differences in biomarker levels. **Results.** The analysis of variance of cerebrospinal fluid biomarkers revealed significant differences in CSF WCC (cells/mm3), Neutrophils (%), Lymphocytes (%), CSF/blood Glucose and Protein ratios in children and adults ($p < 0.05$). However, differences were observed solely in neutrophil levels among elderly subjects. In bacterial meningitis, neutrophil levels increased across all ages, with adults showing higher levels. For meningococcal meningitis, adults had a median neutrophil level of 78.5% [60%, 90%] compared to 57% [24.5%, 85.25%] in children. The CSF white cell count (WCC) median was also higher in adults (339 cells/mm³) compared to children (224 cells/mm³). Viral meningitis cases exhibited higher lymphocyte levels across all age groups, with medians of 69% [34%, 87%] in children, 82% [61%, 93%] in adults, and 77% [55%, 90%] in the elderly. The glucose ratio was lower in bacterial meningitis (<0.3) and higher in viral cases (>0.5). Protein ratios were elevated in bacterial meningitis, indicating increased blood-brain barrier permeability. These results demonstrate a distinct biological profile for different causative agents, modulated by patient age.

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1. INTRODUCTION

Meningitis is an inflammation of the membranes surrounding the brain and spinal cord, often caused by bacterial, viral, fungal, or parasitic infections [1]. Among these, bacterial meningitis is particularly concerning due to its high mortality rate and the severity of its complications. According to the World Health Organization (WHO), bacterial meningitis has the highest fatality rate among the different types, estimated at approximately 10%, although this varies depending on the causative agent, age, and demographics of the patients [2]. It is reported that roughly 20% of individuals diagnosed with bacterial meningitis experience severe complications, resulting in mortality for 1 in 6 cases and serious complications for 1 in 5 survivors [3].

Prompt and accurate diagnosis of meningitis is crucial for initiating appropriate treatment and improving survival rates. Tests on cerebrospinal fluid (CSF), such as culture, Gram stain, and molecular analyses, along with blood tests, are essential for identifying the causative agent and guiding prompt treatment [4]. Cerebrospinal fluid biomarkers play a significant role in diagnosing different types of meningitis, helping to differentiate between bacterial, viral, fungal, or other forms, each with distinct profiles [5]. Biomarker analysis assists clinicians in choosing appropriate antibiotics, antivirals, or antifungals tailored to the identified pathogen. Specific biomarkers also offer insights into infection severity and potential complications, while monitoring treatment response over time.

Meningitis outbreaks, such as the recent one observed in Niger, highlight the importance of a comprehensive understanding and accurate diagnosis of the various forms of meningitis. From 1 November 2022 to 27 January 2023, Niger reported 559 meningitis cases, including 111 confirmed cases and 18 deaths, compared to 231 cases during the same period in 2021-2022. Most of the laboratory-confirmed cases were caused by *Neisseria meningitidis*. The outbreak in Niger is severe and spreading rapidly, posing a high risk of transmission across West Africa, particularly to neighboring countries due to shared borders and concurrent outbreaks. The WHO has classified the outbreak in Niger as high-risk, indicating potential spread throughout Africa [6].

This study aims to conduct a comprehensive investigation into the ranges of laboratory tests present in CSF across various types of meningitis over different populations. Different populations can display diverse responses in biomarkers to infections, influenced by factors like age, genetics, health status, and environmental conditions. Studying these differences helps improve diagnostic accuracy tailored to specific demographics or geographical regions. By comparing CSF laboratory test results across diverse populations and types of meningitis, this research seeks to enhance our understanding of diagnostic variations and improve treatment strategies globally. Ultimately, these insights will contribute to more effective public health interventions and tailored medical responses in managing meningitis outbreaks.

2. MATERIALS AND METHODS

This study was conducted using data on patients diagnosed with meningitis cases reported to SINAN, the Information System on Notifiable Diseases of the Brazilian Government's Health Department, from 2003 to 2022. To assess age-related differences, the full cohort was divided into three major age groups: Children [0-12 years] with 6,408 cases; Adults [13-64 years] with 4,319 cases; and the Elderly [ages ≥ 65 years] with 499 cases. Table 1 presents the distribution of reported cases of meningitis based on the age groups of the affected individuals and the causative agents.

Table 1. Distribution of reported cases of meningitis based on age groups (children, adults and elderly).

Type of causative agent	Children (0-12 years)	Adults (13-64 years)	Elderly (≥ 65 years)
Meningococcaemia	47	31	2
Meningococcal meningitis	68	64	2
Tuberculous meningitis	20	121	7
Haemophilus influenzae meningitis	39	12	1
Pneumococcal meningitis	110	182	25
Aseptic meningitis	5195	2659	257
Meningitis by other bacteria	890	826	172
Meningitis due to other aetiology	39	424	33

Statistical analysis are conducted to uncover nuanced insights within the dataset. This analysis aim to discern patterns, trends, and statistically significant differences in meningitis cases across the specified age groups. The proposed methodology for this study is illustrated in figure 1. A series of statistical analyses are conducted. Descriptive statistics are employed to provide a detailed summary of the distribution and central tendencies of various cerebrospinal fluid biomarkers across different types of meningitis. This allows for a comprehensive understanding of the variations in biomarker levels within each meningitis type. The Welch ANOVA test is performed to explore potential differences in biomarker levels across different meningitis sub-types. Subsequently, the Games-Howell. Post hoc test is employed to discern which specific types of meningitis exhibit significantly different levels of the examined biomarkers. This post hoc test is well-suited for datasets with unequal variances and sample sizes, providing robust comparisons between groups.

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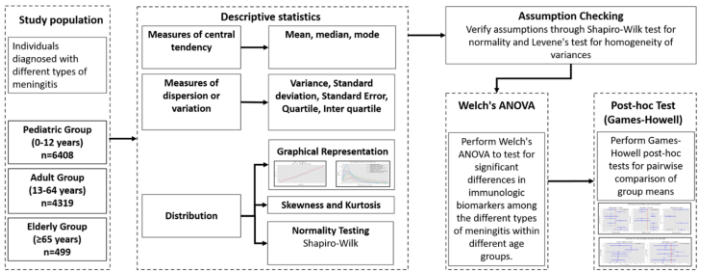

Figure 1. Flowchart illustrating the proposed methodology.

The statistical analyses were implemented using the Python programming language, using the scipy.stats module from the SciPy1 library and the Pingouin2 library. These libraries collectively provide a comprehensive and reliable toolkit for executing descriptive statistics, the Welch ANOVA test, and the Games-Howell post hoc test.

3. RESULTS

The investigation delved into descriptive statistics for various types of meningitis, including Meningococcaemia, Meningococcal meningitis, Tuberculous meningitis, Haemophilus influenzae meningitis, Pneumococcal meningitis, Aseptic meningitis, Meningitis by other bacteria, and Meningitis due to other aetiology. The analysis was stratified across distinct age groups: Children (ages 0-12 years), Adults (ages 13-64 years), and the Elderly (ages ≥ 65 years). Tables 2, 3, and 4 provide detailed overviews of the descriptive statistics for children, adults, and elderly populations, respectively. These tables offer insights into the central tendency and distribution of key variables, including Neutrophils, Lymphocytes, CSF WCC (Cerebrospinal Fluid White Blood Cell Count), CSF/serum Glucose ratio, and CSF/serum Protein ratio among different group ages. The table includes various statistical measures: median, mean ± standard deviation (SD), minimum (min), maximum (max), 25% (First Quartile, Q1), 75% (Third Quartile, Q3), interquartile range (IQR), and 95% confidence intervals (CI).

Figure 2 depicts box plots illustrating the distribution of cerebrospinal fluid biomarkers across different meningitis cases within three populations: children, adults, and elderly individuals. The plots reveal the variability in CSF WCC, neutrophil and lymphocyte levels, Glucose ratios, and Protein ratios among different causative agents, aiding in understanding the diagnostic profiles of meningitis Each plot helps illustrate statistical differences in these biomarkers depending on the causative agent type and age, offering insights into diagnostic profiles and potential disease severity. WCC varies significantly across different types of meningitis. Meningococcal meningitis and Haemophilus influenza meningitis, show higher median values in both populations children and adults, indicating more severe inflammatory responses compared to other types like Meningicoccaemia and aseptic meningitis, which shows lower WCC across all age groups. Neutrophil levels are notably higher in bacterial types of meningitis such as meningococcal, Haemophilus influenzaea, pneumococcal meningitis and meningitis by other bacteria, reflecting a typical acute bacterial response. Lymphocyt counts are more variable across different types. Higher lymphocyte counts in conditions like tuberculous meningitis and viral meningitis (as seen in cases labeled as ”aseptic meningitis”) align with their profiles as predominantly lymphocyte-driven responses. Children tend to show a wider range of lymphocyte counts, particularly in bacterial meningitis such as menincococcaemia, meningococcal and Pneumococcal meningitis as well as Aseptic meningitis, which may indicate a more robust immune response in younger individuals. The Glucose ratio is significantly lower in bacterial meningitis including meningococcal, tuberculous, Haemophilus influenzae meningitis and pneumococcal meningitis, which is consistent with bacterial consumption of Glucose. Elevated Protein ratios are seen in bacterial, indicating a breach in blood-CSF barrier integrity typically associated with these infections [7]. Adults often show higher Protein ratios, possibly due to more severe disease manifestations or comorbidities that affect Protein levels in CSF.

Normality test

Shapiro-Wilk test was employed to assess the normality of the laboratory biomarkers variables in our study. This statistical test evaluates whether the observed data significantly deviates from a normal distribution. The null hypothesis (H_0) states that the data follows a normal distribution, while the alternative hypothesis (H_1) asserts that the data does not follow a normal distribution. A low p-value (< 0.05) indicates a significant departure from normality, leading to the rejection of the null hypothesis. Additionally, skewness was computed for each variable to measure the asymmetry of the distributions. Kurtosis was analyzed to determine the shape of the distribution, with positive kurtosis indicating heavier tails than a normal distribution and negative kurtosis suggesting lighter

tails. The results of normality tests for various features across different types of meningitis, as detailed in Table 5, reveal significant deviations from normal distribution for most variables in pediatric patients. Specifically, neutrophil and lymphocyte levels, as well as CSF WCC, do not follow a normal distribution, indicated by the rejection of the null hypothesis (H0). In contrast, the Glucose ratio CSF/serum is normally distributed for

[1] https://scipy.org

[2] https://pingouin-stats.org/build/html/index.html

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Table 2. Descriptive statistics of CSF biomarkers in pediatric patients within different meningitis.

Type of causative agent	Neutrophils								Lymphocytes								CSF WCC							
	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI
Meningococcaemia	2.00	17.96 ± 27.17	0.00	88.00	0.00	25.00	25.00	9.98 - 25.94	25.00	39.30 ± 41.72	0.00	100.00	0.00	89.50	89.50	27.05 - 51.55	5.00	54.87 ± 163.64	0.00	840.00	2.00	14.50	12.50	6.83 - 102.92
Meningococcal meningitis	57.00	53.46 ± 33.69	0.00	100.00	24.50	85.25	60.75	45.30 - 61.61	13.50	27.76 ± 29.56	0.00	100.00	3.75	45.00	41.25	20.61 - 34.92	224.00	367.63 ± 386.77	0.00	1190.00	39.00	605.00	566.00	274.01 - 461.25
Tuberculous meningitis	15.50	23.25 ± 26.11	0.00	77.00	4.00	35.00	31.00	11.03 - 35.47	65.50	59.95 ± 32.51	0.00	97.00	47.75	84.25	36.50	44.74 - 75.16	88.00	130.95 ± 129.60	0.00	448.00	53.75	173.75	120.00	70.29 - 191.61
Haemophilus influenzae meningitis	71.00	60.05 ± 31.35	0.00	98.00	38.00	83.50	45.50	49.89 - 70.21	23.00	32.97 ± 30.59	0.00	97.00	10.00	48.50	38.50	23.06 - 42.89	320.00	406.08 ± 415.39	0.00	1184.00	59.00	662.50	603.50	271.42 - 540.73
Pneumococcal meningitis	69.00	58.53 ± 30.73	0.00	100.00	40.00	83.00	43.00	52.72 - 64.33	30.00	33.88 ± 30.11	0.00	100.00	7.00	52.00	45.00	28.19 - 39.57	180.50	310.22 ± 329.59	0.00	1250.00	47.00	476.75	429.75	247.93 - 372.50
Aseptic meningitis	19.00	27.02 ± 25.70	0.00	100.00	6.00	42.00	36.00	26.32 - 27.72	69.00	59.95 ± 31.51	0.00	100.00	34.00	87.00	53.00	59.09 - 60.81	76.00	150.01 ± 197.79	0.00	1259.00	30.00	180.00	150.00	144.63 - 155.39
Meningitis by other bacteria	68.00	60.16 ± 26.64	0.00	100.00	46.00	80.00	34.00	58.41 - 61.91	25.00	31.21 ± 25.21	0.00	100.00	12.00	45.00	33.00	29.55 - 32.87	195.00	322.18 ± 320.50	0.00	1234.00	65.25	491.50	426.25	301.09 - 343.26
Meningitis due to other aetiology	6.00	17.77 ± 25.60	0.00	97.00	3.00	19.00	16.00	9.47 - 26.07	82.00	66.77 ± 35.14	0.00	99.00	44.50	94.50	50.00	55.38 - 78.16	131.00	276.38 ± 336.27	3.00	1024.00	19.00	355.00	336.00	167.38 - 385.39

Type of causative agent	Glucose ratio CSF/serum								Protein ratio CSF/serum							
	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI
Meningococcaemia	0.65	0.62 ± 0.20	0.11	0.99	0.49	0.77	0.28	0.56 - 0.68	0.21	0.37 ± 0.46	0.10	2.81	0.18	0.31	0.14	0.24 - 0.51
Meningococcal meningitis	0.27	0.36 ± 0.29	0.01	1.06	0.09	0.64	0.55	0.29 - 0.43	1.26	1.27 ± 0.91	0.02	3.61	0.41	1.90	1.49	1.05 - 1.50
Tuberculous meningitis	0.29	0.32 ± 0.20	0.02	0.80	0.21	0.35	0.14	0.22 - 0.41	1.43	1.60 ± 0.96	0.31	3.35	0.85	2.46	1.61	1.15 - 2.05
Haemophilus influenzae meningitis	0.18	0.23 ± 0.22	0.01	0.80	0.05	0.36	0.31	0.16 - 0.30	1.76	1.61 ± 0.89	0.01	3.19	1.01	2.29	1.29	1.32 - 1.90
Pneumococcal meningitis	0.16	0.22 ± 0.22	0.00	0.81	0.04	0.37	0.33	0.18 - 0.27	1.61	1.65 ± 0.96	0.00	3.52	1.00	2.40	1.40	1.47 - 1.83
Aseptic meningitis	0.57	0.57 ± 0.14	0.00	1.07	0.50	0.65	0.15	0.57 - 0.58	0.35	0.47 ± 0.42	0.00	3.63	0.25	0.54	0.29	0.46 - 0.49
Meningitis by other bacteria	0.53	0.50 ± 0.21	0.00	1.07	0.39	0.63	0.24	0.48 - 0.51	0.61	0.91 ± 0.79	0.00	3.63	0.36	1.25	0.89	0.86 - 0.96
Meningitis due to other aetiology	0.48	0.48 ± 0.23	0.05	0.94	0.37	0.58	0.20	0.41 - 0.55	0.63	0.87 ± 0.76	0.12	3.15	0.23	1.05	0.82	0.63 - 1.12

Table 3. Descriptive statistics of CSF biomarkers in adults patients within different meningitis.

Type of causative agent	Neutrophils								Lymphocytes								CSF WCC							
	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI
Meningococcaemia	1.00	22.77 ± 33.50	0.00	95.00	0.00	57.00	57.00	10.48 - 35.06	21.00	37.16 ± 39.03	0.00	100.00	0.00	68.00	68.00	22.84 - 51.48	5.00	35.55 ± 89.01	0.00	400.00	1.00	14.50	13.50	2.90 - 68.20
Meningococcal meningitis	78.50	68.59 ± 28.44	0.00	100.00	60.00	90.00	30.00	61.49 - 75.70	16.00	24.75 ± 25.05	0.00	100.00	5.75	33.50	27.75	18.49 - 31.01	339.00	376.61 ± 362.81	0.00	1225.00	25.00	640.00	615.00	285.98 - 467.24
Tuberculous meningitis	20.00	29.94 ± 27.75	0.00	97.00	7.00	50.00	43.00	24.95 - 34.94	69.00	59.38 ± 31.87	0.00	100.00	38.00	87.00	49.00	53.64 - 65.12	150.00	204.07 ± 205.98	0.00	1200.00	60.00	277.00	217.00	166.99 - 241.14
Haemophilus influenzae meningitis	80.00	63.75 ± 32.33	12.00	99.00	35.50	88.50	53.00	43.21 - 84.29	17.00	30.08 ± 28.10	1.00	71.00	9.25	63.50	54.25	12.23 - 47.94	344.50	392.83 ± 340.20	15.00	880.00	26.50	681.25	654.75	176.68 - 608.98
Pneumococcal meningitis	80.00	70.45 ± 27.72	0.00	100.00	60.00	91.00	31.00	66.40 - 74.50	15.00	21.79 ± 23.37	0.00	100.00	5.00	28.00	23.00	18.37 - 25.21	285.00	422.79 ± 373.08	0.00	1260.00	110.00	677.50	567.50	368.22 - 477.36
Aseptic meningitis	10.00	18.31 ± 22.23	0.00	99.00	3.00	25.00	22.00	17.46 - 19.15	82.00	71.74 ± 28.88	0.00	100.00	61.00	93.00	32.00	70.64 - 72.84	106.00	195.84 ± 228.35	0.00	1215.00	35.00	277.00	242.00	187.15 - 204.52
Meningitis by other bacteria	66.00	60.42 ± 28.16	0.00	100.00	47.00	83.00	36.00	58.50 - 62.35	28.00	33.35 ± 26.69	0.00	100.00	12.00	45.00	33.00	31.53 - 35.17	234.50	362.68 ± 347.70	0.00	1255.00	64.25	563.75	499.50	338.94 - 386.43
Meningitis due to other aetiology	8.00	20.07 ± 25.67	0.00	100.00	2.00	30.00	28.00	17.62 - 22.52	76.50	59.77 ± 37.23	0.00	100.00	21.75	92.00	70.25	56.22 - 63.32	60.00	134.32 ± 188.20	0.00	1215.00	19.00	174.25	155.25	116.36 - 152.29

Type of causative agent	Glucose ratio CSF/serum								Protein ratio CSF/serum							
	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI
Meningococcaemia	0.61	0.53 ± 0.22	0.00	0.85	0.42	0.69	0.27	0.45 - 0.62	0.39	0.80 ± 0.91	0.00	3.60	0.24	0.93	0.69	0.47 - 1.13
Meningococcal meningitis	0.28	0.30 ± 0.23	0.01	1.04	0.11	0.46	0.35	0.24 - 0.36	1.23	1.34 ± 0.96	0.00	3.62	0.49	2.02	1.53	1.10 - 1.58
Tuberculous meningitis	0.28	0.34 ± 0.23	0.01	1.04	0.17	0.43	0.26	0.30 - 0.38	1.82	1.82 ± 0.88	0.15	3.63	1.17	2.60	1.43	1.66 - 1.98
Haemophilus influenzae meningitis	0.28	0.43 ± 0.35	0.00	1.05	0.18	0.77	0.60	0.21 - 0.65	1.07	1.38 ± 0.97	0.33	3.41	0.73	1.92	1.20	0.77 - 2.00
Pneumococcal meningitis	0.12	0.22 ± 0.23	0.00	1.03	0.04	0.37	0.33	0.19 - 0.26	1.55	1.57 ± 0.96	0.00	3.52	0.81	2.27	1.45	1.43 - 1.71
Aseptic meningitis	0.56	0.56 ± 0.17	0.00	1.07	0.47	0.66	0.19	0.56 - 0.57	0.67	0.84 ± 0.61	0.00	3.64	0.42	1.06	0.64	0.81 - 0.86
Meningitis by other bacteria	0.46	0.44 ± 0.24	0.00	1.06	0.25	0.61	0.36	0.43 - 0.46	1.07	1.27 ± 0.84	0.00	3.64	0.61	1.74	1.13	1.21 - 1.33
Meningitis due to other aetiology	0.35	0.36 ± 0.19	0.00	1.04	0.23	0.48	0.25	0.34 - 0.38	0.89	1.05 ± 0.73	0.00	3.60	0.49	1.45	0.96	0.98 - 1.12

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Table 4. Descriptive statistics of CSF biomarkers in elderly patients within different meningitis.

Type of causative agent	Neutrophils								Lymphocytes								CSF WCC							
	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI
Pneumococcal meningitis	75.00	71.24 ± 29.80	0.00	100.00	60.00	94.00	34.00	58.94 - 83.54	14.00	18.32 ± 20.56	0.00	84.00	2.00	30.00	28.00	9.83 - 26.81	160.00	292.44 ± 333.74	6.00	1046.00	48.00	341.00	293.00	154.68 - 430.20
Aseptic meningitis	10.00	22.92 ± 26.38	0.00	97.00	3.00	35.00	32.00	19.68 - 26.16	77.00	65.83 ± 31.93	0.00	100.00	55.00	90.00	35.00	61.91 - 69.75	74.00	147.11 ± 187.14	1.00	1200.00	30.00	180.00	150.00	124.12 - 170.10
Meningitis by other bacteria	75.00	65.82 ± 26.42	0.00	97.00	52.75	87.25	34.50	61.84 - 69.80	20.00	28.53 ± 23.68	0.00	96.00	11.00	39.25	28.25	24.96 - 32.09	210.00	333.44 ± 329.62	0.00	1260.00	77.75	476.75	399.00	283.83 - 383.05
Meningitis due to other aetiology	16.00	27.30 ± 27.66	0.00	95.00	3.00	46.00	43.00	17.49 - 37.11	75.00	60.91 ± 31.77	0.00	100.00	32.00	87.00	55.00	49.64 - 72.18	97.00	224.88 ± 280.94	0.00	970.00	47.00	272.00	225.00	125.26 - 324.50

Type of causative agent	Glucose ratio CSF/serum								Protein ratio CSF/serum							
	median	mean ± sd	min	max	25%	75%	IQR	95% CI	median	mean ± sd	min	max	25%	75%	IQR	95% CI
Pneumococcal meningitis	0.08	0.17 ± 0.25	0.00	0.94	0.01	0.14	0.13	0.06 - 0.27	1.54	1.56 ± 0.88	0.18	3.58	0.86	1.90	1.04	1.19 - 1.92
Aseptic meningitis	0.60	0.60 ± 0.24	0.00	1.07	0.43	0.74	0.31	0.57 - 0.63	0.80	1.04 ± 0.80	0.00	3.63	0.47	1.35	0.88	0.95 - 1.14
Meningitis by other bacteria	0.53	0.50 ± 0.29	0.01	1.06	0.26	0.73	0.47	0.46 - 0.54	1.36	1.47 ± 0.81	0.00	3.58	0.85	1.98	1.13	1.34 - 1.59
Meningitis due to other aetiology	0.30	0.30 ± 0.19	0.00	0.68	0.18	0.44	0.26	0.23 - 0.36	0.83	1.01 ± 0.72	0.00	3.48	0.63	1.05	0.42	0.76 - 1.27

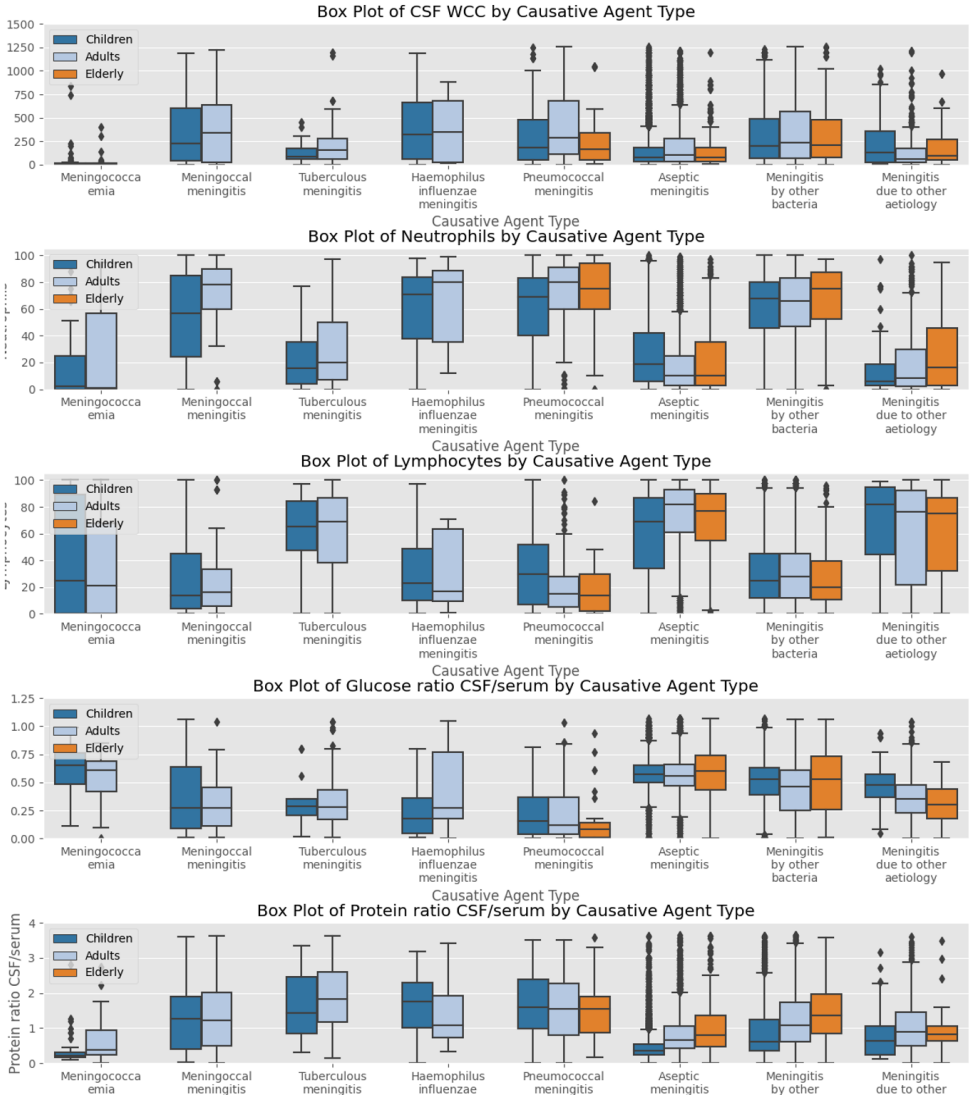

Figure 2. Box plots illustrating the distribution of cerebrospinal fluid biomarkers across different meningitis cases in three distinct age groups.

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Meningococcaemia, Haemophilus influenzae meningitis, and Meningitis due to other aetiology, with the null hypothesis not rejected. The Protein ratio CSF/serum also follows a normal distribution for Tuberculous meningitis and Haemophilus influenzae meningitis. In adults population, Neutrophils, Lymphocytes, Glucose ratio CSF/serum, CSF WCC, and Protein ratio across all causative agents show a rejection of the null hypothesis (H_0), indicating non-normal distribution. However, for Haemophilus influenzae meningitis, the Glucose ratio, CSF WCC, and Protein ratio data fail to reject the null hypothesis (H_0), suggesting a normal distribution, yet interpretation may be limited due to the low Shapiro-Wilk test power for small sample sizes [8]. Samples with a size of fewer than 7 were excluded from the study involving the elderly population. Table 5 indicates deviations from normality across various features for different causative agents, except for the Protein ratio in Pneumococcal meningitis and the Glucose ratio in Meningitis due to other aetiologies within elderly population.

Table 5. Statistical features of various causative agents in meningitis by population, including sample size, kurtosis, skewness, and shapiro-wilk test results for normality. Each row represents a specific causative agent and population group, with columns detailing the associated statistical attributes.

Type of causative agent	Population	Sample Size	Feature	Kurtosis	Skewness	Shapiro-Wilk Test Statistic	Shapiro-Wilk Test P-Value
Meningococcemia	Children	47	Glucose ratio CSF/serum	-0.33	-0.39	0.98	0.45
Tuberculous meningitis	Children	20	Protein ratio CSF/serum	-1.14	0.43	0.93	0.14
Hemophilus influenzae meningitis	Children	39	Protein ratio CSF/serum	-0.78	-0.15	0.96	0.26
	Adults		Glucose ratio CSF/serum	-1.23	0.46	0.9	0.16
		12	CSF WCC	-1.66	0.22	0.88	0.08
			Protein ratio CSF/serum	0.05	0.8	0.91	0.22
Pneumococcal meningitis	Elderly	25	Protein ratio CSF/serum	0.19	0.67	0.95	0.22
Meningitis due to other etiology	Children	39	Glucose ratio CSF/serum	-0.12	0.21	0.96	0.19
	Elderly	33	Glucose ratio CSF/serum	-0.76	0.34	0.96	0.2

Analysis of variance

In consideration of the potential non-homogeneity of variances assumption (see Figure 2), Welch ANOVA (Analysis of Variance) was employed as an alternative due to its capability to generate reliable results in situations characterized by unequal variances across the studied groups [9]. This test was conducted to explore potential differences in biomarker levels among various types of meningitis across different age groups. Table 6 presents a detailed summary of the Welch ANOVA analysis results, including the statistical significance of differences in dependent variables across different types of meningitis considered in this study. Each row corresponds to a specific variable, displaying the F-statistic, p-value, and effect size (η^2_p). The significance is determined by whether the p-value is less than 0.05, suggesting a statistically significant difference between groups and supporting the rejection of the null hypothesis (H_0: No difference among groups). If the means show significant differences (p-value > 0.05), this supports the alternative hypothesis (H_1: There are differences among groups). Statistically significant differences were observed in various biomarkers (CSF WCC, Neutrophils, Lymphocytes, Glucose ratio CSF/serum, and Protein ratio CSF/serum) across different causative agent groups within children and adults. For elderly population, significant differences were observed only in Neutrophil levels. This suggests that the impact of causative agents on these biomarkers may be different or negligible in the elderly compared to children and adults. The partial eta-squared (η^2_p) values indicate the proportion of variance explained by causative agent groups in biomarker levels [10]. Higher values suggest stronger effects, aiding in understanding the impact of causative agents across populations. Effect sizes for certain biomarkers vary across age groups. For example, Neutrophils exhibit higher effect sizes in adults and the elderly compared to children. This indicates that the impact of causative agents on Neutrophil levels is more pronounced in older age groups.

Table 6. Welch's ANOVA results for different biomarkers across populations.

Dependent Variable	Population	F-statistic[3]	p-value	η^2_p	Significance
CSF WCC	children	44.73	0.00	0.008	The means of CSF WCC vary significantly across different types of meningitis in both population.
	adults	58.72	0.00	0.10	
	elderly	0.00	1.00	0.11	Means of CSF WCC are likely equal between meningitis types in elderly population.
Neutrophils	children	188.56	0.00	0.19	The means of Neutrophils levels vary significantly across different types of meningitis in all three populations
	adults	305.53	0.00	0.38	
	elderly	170.58	0.00	0.40	Elderly population shows a higher amount of variance (40%).
Lymphocytes	children	260.61	0.00	0.26	The means of Lymphocytes levels vary significantly across different types of meningitis in both population.
	adults	144.37	0.00	0.11	Pediatric patients explains a higher amount of variance (26%) compared to adults (11%)
	elderly	0.00	1.00	0.31	Means of Lymphocytes levels are likely equal between meningitis types in elderly population.
Glucose ratio CSF/serum	children	134.48	0.00	0.2	The means of Glucose ratio vary significantly across different types of meningitis in both population.
	adults	73.43	0.00	0.14	Pediatric patients explains a higher amount of variance (20%) compared to adults (14%)
	elderly	0.00	1.00	0.18	Means of Glucose ratio are likely equal between meningitis types in elderly population.
Protein ratio CSF/serum	children	59.51	0.00	0.12	The means of Protein ratio vary significantly across different types of meningitis in both population.
	adults	78.29	0.00	0.18	Adults patients explains a slightly higher amount of variance (18%) than in pediatric population (12%)
	elderly	0.00	1.00	0.09	Means of Protein ratio are likely equal between meningitis types in elderly population.

Post hoc test

Games-Howell post hoc test is employed to identify specific pairs of meningitis types that exhibited statistically significant differences in biomarker levels. This post hoc analysis, well-suited for data with unequal variances and sample sizes [11], facilitated a nuanced understanding of the variations in biomarker concentrations among different meningitis categories. Notably, the Games-Howell test revealed distinct patterns of significance, specify which pairs of meningitis types demonstrated significant differences in biomarker levels. These findings contribute valuable insights into the central tendencies and distributions of key

[3] Degrees of freedom between groups (ddof) = 7 for all populations

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variables, and provide a better understanding of the heterogeneity within the studied meningitis sub-types across different age groups. This study involves comparing mean differences in different biomarkers levels among all types of meningitis of this study. Multiple comparisons are made among means of groups with unequal variances and sample size and another group that is compared against it. The zero-difference line indicates no difference between groups. Points to the right suggest the first group has higher means; points to the left indicate the second group has higher means. In the examination of white cell count parameters in the pediatric population (Figure 3(A)), Meningococcal meningitis (group 2) significantly differs from Aseptic meningitis (group 6), displaying a mean difference of 217.62 (95% CI: 147.68,

158.14). Similarly, Haemophilus influenzae meningitis (group 4) exhibits a substantial difference in white cell count from Aseptic meningitis (group 6), with a mean difference of 256.07 (95% CI: 146.45, 157.61). Significant mean differences are observed between Meningococcaemia (group 1) and Haemophilus influenza meningitis (group 4) -351.20 (95% CI: 137.86; 288.34). In our analysis, the confidence intervals that are very close to the zero reference line on the forest plot are not considered, as these values may suggest a potential lack of statistical significance or effect. In the analysis of the adult population, Pneumococcal meningitis (group 5) demonstrates a significant mean difference of 226.95 (95% CI: 201.7, 219.80) from Aseptic meningitis (group 6). Furthermore, Meningococcal meningitis (group 2) versus Meningitis due to other etiology (group 8) reveals a mean difference of 242.29 (95% CI: 145.02, 187.05), emphasizing notable distinctions. Pneumococcal meningitis (group 5) versus Meningitis due to other etiology (group 8) shows a substantial mean difference of 288.47 (95% CI: 198.55, 245.06).

Based on the results of the Games-Howell test (Figure 3(B)), significant mean differences and their associated confidence intervals suggest that neutrophil levels in Meningococcal meningitis (group 2) and Haemophilus influenzae meningitis (group 4) are statistically different from those in Meningitis due to other etiologies (group 8) in the children's population. In the adult population, distinct neutrophil responses were observed across various types of meningitis. Aseptic meningitis (group 6) showed a significant mean decrease of -42.12 in neutrophil levels compared to meningitis by other bacteria (group 7). Neutrophil levels in Haemophilus influenzae meningitis (group 4) differ significantly from both Meningitis due to other etiology (group 8) 43.68 (95% CI: 18.78, 23.71) and Aseptic meningitis (group 6) 45.44 (95% CI: 17.69, 19.31). Meningococcal meningitis (group 2) also shows significant differences in neutrophil levels compared to Meningitis due to other etiology (group 8) 48.52 (95% CI: 23.71, 29.27) and Aseptic meningitis (group 6) 50.29 (95% CI: 18.61, 20.39). Pneumococcal meningitis (group 5) demonstrates significant differences in neutrophil levels compared to Meningitis due to other etiology (group 8) 50.38 (95% CI: 32.39, 37.94) and Aseptic meningitis (group 6) 52.14 (95% CI: 20.72, 22.58). In the elderly population, the results indicate neutrophil responses when affected by Pneumococcal meningitis (group 5) compared to other etiologies (group 8), and Aseptic meningitis (group 6).

The test results indicate significant mean differences in Lymphocytes levels only in adults (See figure 3(C)) between Tuberculous meningitis (group 3) and Pneumococcal meningitis (group 5) with mean difference of 37.59 (95% CI: 33.18, 40.46).

The Glucose ratio in cerebrospinal fluid/serum was examined in both pediatric and adult populations (Figure 3(D)). In children, the comparison between Meningococcaemia (group 1) and Pneumococcal meningitis (group 5) revealed a mean difference of 0.40 (95% CI: 0.30, 0.39). Similarly, in adults, the corresponding mean difference was 0.31 (95% CI: 0.23, 0.30). These findings suggest notable differences in the Glucose ratio between the two specified meningitis types across age groups.

The analysis of Protein ratios in cerebrospinal fluid/serum among pediatric subjects, revealed distinct patterns across diverse cases of meningitis (Figure 3(E)). Meningococcal meningitis (group 2), Tuberculous meningitis (group 3), Haemophilus influenza meningitis (group 4) and Pneumococcal meningitis (group 5), demonstrated a mean difference of 0.80 (95% CI: 0.47, 0.50), 1.13 (95% CI: 0.47, 0.49), 1.14 (95% CI: 0.47, 0.50) and 1.18 (95% CI: 0.49, 0.51) relative to Aseptic meningitis (group 6) respectively. Comparisons involving Meningoccaemia (group 1) unveiled inverse Protein ratios of -1.23 (95% CI: 0.55, 0.95) and -1.24 (95% CI: 0.75, 1.13) with Tuberculous meningitis (group 3) and Haemophilus influenzae meningitis (group 4), respectively. Negative values suggest a lower Protein ratio in Meningococcemia compared to the other types of meningitis being compared. In adults, the specific comparison of Tuberculous meningitis with Aseptic meningitis demonstrated a mean difference of 0.99 (95% CI: 0.85, 0.90), illustrating distinct Protein ratio patterns in this age group.

4. DISCUSSION

This study aim to compare the neutrophils and lymphocytes counts, CSF WCC, Glucose and Protein ratio (CSF/serum) among patients with different types of meningitis, stratified by age groups. The findings provide insights into the immune response profiles and biochemical characteristics associated with various types of meningitis. In cases of bacterial meningitis (including Meningococcal, Tuberculous, *Haemophilus influenzae*, Pneumococcal, and other bacterial etiologies), there was a marked increase in neutrophil levels across all age groups. This aligns with the established understanding that bacterial infections typically elicit a robust neutrophilic response. Neutrophil levels were generally higher in adults compared to

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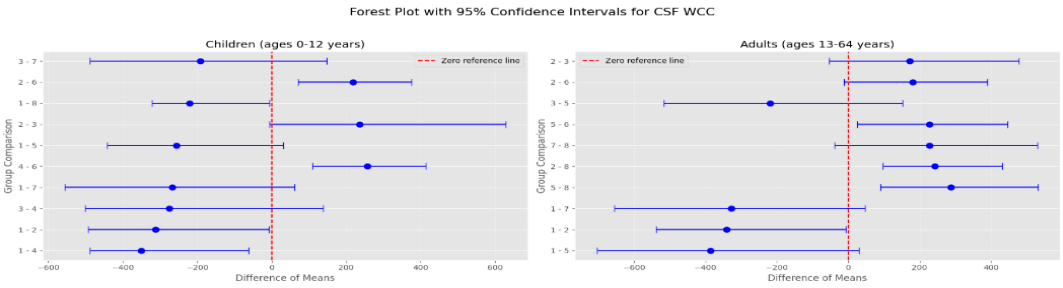
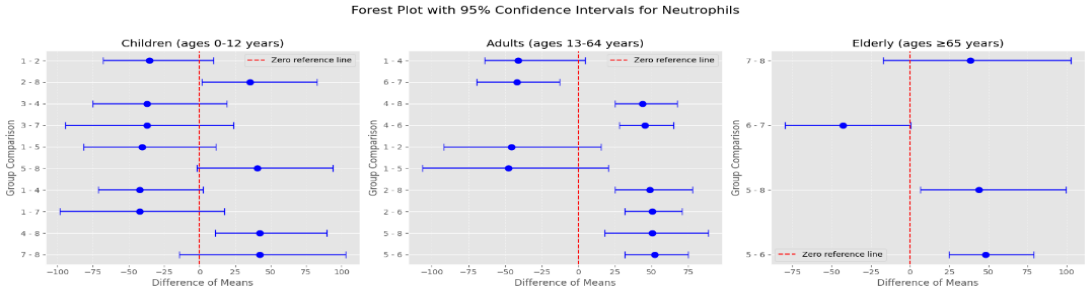
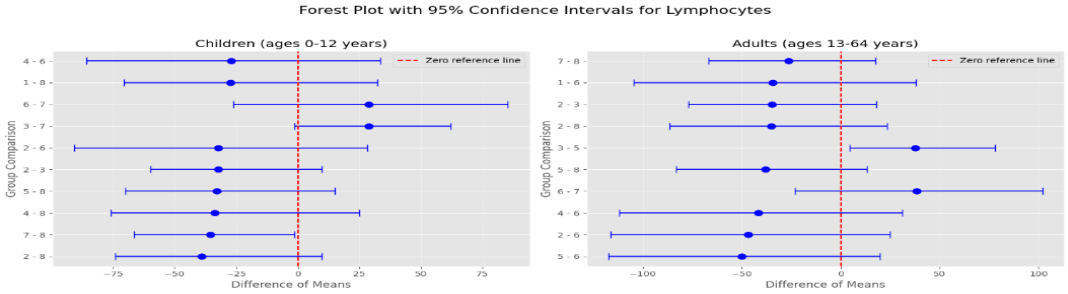


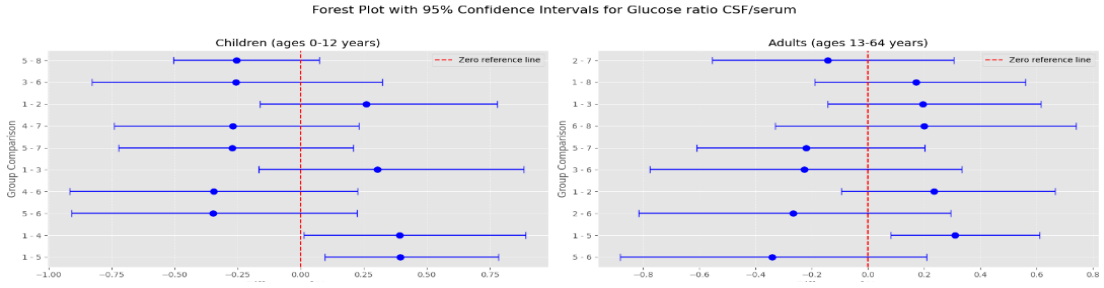
(A) Forest plot comparing CSF WCC across different age groups



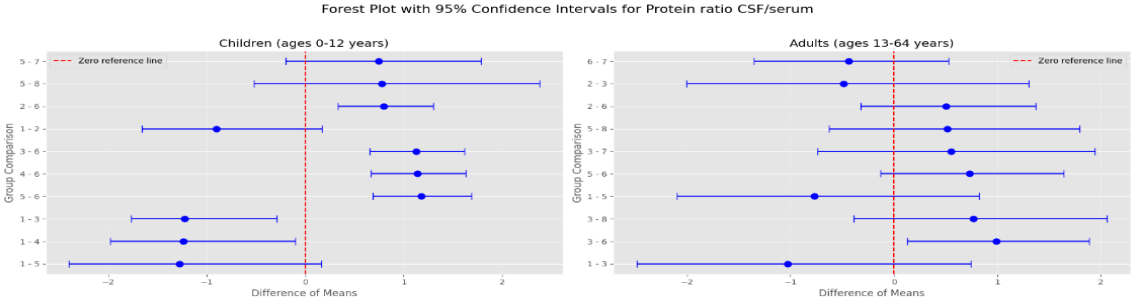
(B) Forest plot comparing Neutrophils level across different age groups



(C) Forest plot comparing Lymphocytes level across different age groups



(D) Forest plot comparing Glucose ratio across different age groups



(E) Forest plot comparing Protein ratio across different age groups

Figure 1. Forest plot comparing different attributes across different age groups with 95% confidence intervals

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children in conditions like Meningococcal meningitis. For instance, adults with Meningococcal meningitis had a median neutrophil level of 78.5% [60%, 90%], compared to 57% [24.5%, 85.25%] in children. This could reflect differences in immune system maturity and response mechanisms. Viral meningitis cases showed higher lymphocyte levels, consistent with viral infections typically inducing a lymphocytic response. The median lymphocyte level was notably higher among children 69% [34%, 87%], adults 82% [61%, 93%], and elderly 77% [55%, 90%] with aseptic meningitis compared to those with bacterial meningitis. While lymphocyte levels were generally higher in adults than in children for viral infections, the differences were less pronounced compared to bacterial infections. CSF WCC was significantly elevated in bacterial meningitis cases, particularly in adults. For instance, the median CSF WCC in children with Meningococcal meningitis was 224 cells/mm^3, compared to 339 cells/mm^3 in adults. This elevation is indicative of the intense inflammatory response to bacterial pathogens. In viral meningitis, CSF WCC was elevated but generally lower than in bacterial cases. This reflects the typically less intense inflammatory response seen in viral infections. The CSF WCC in patients with meningococcemia tends to be relatively low in both children and adults. For children with meningococcemia, the median CSF WCC was 5 cells/mm^3, with a mean ± SD of 54.87 ± 163.64 cells/mm^3. The range was from 0 to 840 cells/mm^3. Despite some extreme values, the central tendency (median) remained low. For adults aged 13-64 years, the median CSF WCC was also 5 cells/mm^3, with a mean ± SD of 35.55 ± 89.01 cells/mm^3. The range extended from 0 to 400 cells/mm^3. Meningococcemia is primarily a bloodstream infection. The bacteria can cause sepsis without necessarily leading to meningitis, where CSF WCC would be expected to rise significantly resulting in a lower CSF WCC. This highlights the importance of considering other clinical factors and diagnostic tools when evaluating and managing patients with suspected meningococcemia. The Glucose ratio was notably lower in bacterial meningitis including Meningococcal, Tuberculosis, *Haemophilus influenzae*, and Pneumococcal meningitis, with values often below 0.3, reflecting the consumption of Glucose by bacteria in the CSF. In viral meningitis, the Glucose ratio was higher, often above 0.5. The Protein ratio was higher in bacterial meningitis including Meningococcal, Tuberculosis, *Haemophilus influenzae*, and Pneumococcal meningitis, reflecting increased permeability of the blood-brain barrier and Protein leakage into the CSF. Building on the scoring tool established by Pascal Chavanet et al. for pediatric and adult meningitis, where a CSF WCC >1700 cells/mm^3, CSF neutrophil percentage >80%, CSF Protein >2.3 g/L, and Glucose CSF/blood ratio <0.33 are identified as key indicators of bacterial etiology in adults, and a CSF WCC >1800 cells/mm^3, CSF neutrophil percentage >80%, CSF Protein >1.2 g/L, and Glucose CSF/blood ratio <0.3 in children, our findings align closely with these thresholds. We observed significantly elevated CSF WCC and Protein ratios, along with low Glucose ratios, in bacterial meningitis cases, thus reinforcing these diagnostic criteria [12]. Sérgio Monteiro de Almeida et al. compared the effectiveness of lactate and Glucose (GL) in CSF, as well as the CSF/blood GL ratio, in distinguishing between acute bacterial meningitis (BM) and viral meningitis (VM) with typical and atypical CSF characteristics. They observed that the median WCC was significantly higher in bacterial meningitis (560 × 10^6/L) compared to viral meningitis (36 × 10^6/L). Additionally, the median neutrophil percentage was markedly higher in bacterial meningitis (83%) than in viral meningitis (10%). The Glucose ratio was also different, with a median of 0.30 in bacterial meningitis and 0.56 in viral meningitis [5]. Despite the valuable insights gained from our data, its specific regional focus may limit the generalizability of our findings to broader populations. Additionally, the interpretation of CSF parameters can be influenced by factors such as the timing of lumbar puncture, prior antibiotic therapy, and the presence of other infections. These factors highlight the need for careful consideration in diverse clinical settings and underscore the importance of future research to further validate and expand upon our findings. Furthermore, it is necessary to compare other biomarkers, such as CSF lactate, as it had demonstrated superior operational characteristics compared to CSF Glucose in differentiating between bacterial and viral meningitis [5].

5. CONCLUSION

This study underscores the importance of comprehensive CSF analysis in the management of meningitis. Significant variations in biomarker levels were evident across different causative agents among children and adults. Conversely, the elderly population showed less variability in several biomarkers, highlighting potential age-related differences in meningitis presentations. By elucidating the distinct immune responses and biochemical profiles associated with different types of meningitis across age groups, clinicians can enhance diagnostic precision and optimize patient care. Further research could explore the underlying mechanisms driving these age-related differences in immune response, potentially leading to targeted therapeutic interventions.

Data availability statement: The SINAN database can be accessed at https://datasus.saude.gov.br/transferencia-de-arquivos/#

Competing interests: The authors declare that they have no competing interest.

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REFERENCES

1. Shmaefsky, B., & Babcock, H. (2010). Meningitis. Infobase Publishing.
2. Tetsuya Akaishi, Kunio Tarasawa, Kiyohide Fushimi, Nobuo Yaegashi, Masashi Aoki, and Kenji Fujimori. Demographic profiles and risk factors for mortality in acute meningitis: A nationwide population-based observational study. Acute Medicine & Surgery, 11(1):e920, 2024.
3. Meningitis — who.int. www.who.int/news-room/fact-sheets/detail/meningitis. [Accessed 11-06-2024].
4. Taojun He, Samuel Kaplan, Mini Kamboj, and Yi-Wei Tang. Laboratory diagnosis of central nervous system infection. Current infectious disease reports, 18:1–12, 2016.
5. Sérgio Monteiro de Almeida, Suélen Maria Parizotto Furlan, Arianne Maris Munhoz Cretella, Bruna Lapinski, Keite Nogueira, Laura Lucia Cogo, Luine Rosele Renaud Vidal, and Meri Bordignon Nogueira. Comparison of cerebrospinal fluid biomarkers for differential diagnosis of acute bacterial and viral meningitis with atypical cerebrospinal fluid characteristics. Medical Principles and Practice, 29(3):244–254, 2020.
6. Meningitis — who.int. https://www.who.int/emergencies/disease-outbreak-news/item/2023-DON439. [Accessed 14-06-2024].
7. Rosanna Herold, Horst Schroten, and Christian Schwerk. Virulence factors of meningitis-causing bacteria: Enabling brain entry across the blood–brain barrier. International Journal of Molecular Sciences, 20(21), 2019.
8. Nornadiah Mohd Razali, Yap Bee Wah, et al. Power comparisons of shapiro-wilk, kolmogorov-smirnov, lilliefors and anderson-darling tests. Journal of statistical modeling and analytics, 2(1):21–33, 2011.
9. Yuhang Zhou, Yiyang Zhu, andWeng KeeWong. Statistical tests for homogeneity of variance for clinical trials and recommendations. Contemporary Clinical Trials Communications, page 101119, 2023.
10. José Valladares-Neto. Effect size: A statistical basis for clinical practice. Revista Odonto Ciência, 33(1):84–90, 2018.
11. Shayna A Rusticus and Chris Y Lovato. Impact of sample size and variability on the power and type i error rates of equivalence tests: A simulation study. Practical Assessment, Research, and Evaluation, 19(1):11, 2019.
12. Pascal Chavanet, C´eline Schaller, Corine Levy, Juan Flores-Cordero, Max Arens, Lionel Piroth, Edouard Bingen, and Henri Portier. Performance of a predictive rule to distinguish bacterial and viral meningitis. Journal of Infection, 54(4):328–336, 2007.

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