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ORIGINAL RESEARCH

Prognostic factors in pediatric pneumococcal meningitis patients in mainland China: a retrospective multicenter study

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Background: Prognosis of pneumococcal meningitis (PM) remains very poor, especially in less developed countries. Currently, few multi-centric studies on pediatric PM have been reported in mainland China.

Objectives: This study aimed to explore the correlation of clinical and laboratory findings with complications and prognosis in pediatric PM.

Methods: The pediatric PM patients were retrospectively recruited from ten pediatric tertiary hospitals across China between January 2013 and June 2018. Clinical, biochemical, and microbiological data and follow-up information were collected. Predictive factors for complications and prognostic factors for overall survival (OS) and sequelae-free survival (SFS) were analyzed.

Results: A total of 132 pediatric PM patients were included. Seventy-one patients had complications, 25 patients died, and 39 patients had neurological sequelae. Multivariate logistic regression suggested that age less than 28 months (adjusted OR=2.654, 95% CI=1.067–6.600, *P*=0.036) and lower white blood cells in blood (aOR=3.169, 95% CI=1.395–7.202, *P*=0.006) were associated with high risk of complications. Multivariate Cox's proportional hazard regression suggested that age less than 28 months (aHR=6.479, 95%CI=1.153–36.404, *P*=0.034), coma (aHR=9.808, 95%CI=2.802–34.323, *P*=0.000), and non-adjuvant steroid therapy (aHR=4.768 95%CI=1.946–11.678, *P*=0.001) were independent prognostic factors for poor OS; coma (aHR=5.841, 95%CI=2.652–12.864, *P*=0.000), septic shock on admission (aHR=2.949, 95%CI=1.049–8.290, *P*=0.040), and lower glucose level in cerebrospinal fluid (CSF) (aHR=2.523, 95%CI=1.336–4.765, *P*=0.004) were independent prognostic factors for poor SFS.

Conclusion: Age, coma, and adjuvant steroid therapy were independent factors for OS, while coma, septic shock on admission, and lower glucose level in CSF were independent factors for SFS in pediatric PM patients. These factors might be used to identify PM patients with poor prognosis and guide individual treatment.

Keywords: pneumococcal meningitis, clinical findings, complication, prognosis, pediatric

Introduction

Streptococcus pneumoniae is a common cause of meningitis and pneumococcal meningitis (PM) accounts for 50% of bacterial meningitis globally.[1,2] PM is also a common bacterial meningitis in China.[3] Most PM patients present with a headache, neck stiffness, and fever.[4] Culture of cerebrospinal fluid (CSF) obtained from a lumbar puncture should be performed to confirm the diagnosis of PM.

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In spite of progress in diagnosis, antibiotic therapy strategies, and intensive care, PM is associated with a mortality rate of 6%–17% in high-income countries including US and some European countries.[5–8] However, in developing countries and regions such as sub-Saharan Africa, the mortality of PM patients has been reported to be as high as 73%.[7,9–13] Among surviving patients, 25%–63% suffer from long-term neurological sequelae,[5,9,14,15] which significantly affect the quality of life of survivors.

Early identification of patients with poor prognosis contributes to individualized treatment and more aggressive therapeutic strategies. A series of clinical features, biochemical, and microbiological factors have been identified as prognostic factors in PM. The most important prognostic factors associated with mortality of PM patients include C-reactive protein,[5] age,[16,17] score on SOFA, Glasgow Score, severe hypoglycorrhachia,[17] corticosteroid treatment,[18] and glucose in CSF.[19] And the most important prognostic factors in relation to neurological handicaps seem to be hypoglycorrhachia,[20–24] shock, coma and convulsions on admission or during hospitalization,[25] mechanical ventilation requirement, late diagnosis, ataxia, and steroid treatment.[26]

However, these studies are mainly performed in European and American countries and limited to a few research centers. Further multicenter research is required to verify the prognostic value of these factors and improve clinical management of PM patients in mainland China. The present study aimed to recruit pediatric PM patients retrospectively from multiple hospitals in mainland China and investigate the risk factors of complications as well as the prognostic factors of overall survival (OS) and neurological sequelae-free survival (SFS) in pediatric PM patients.

Methods

Participants

A multicenter retrospective study was performed to consecutively recruit pediatric PM patients between January 2013 to June 2018 from ten pediatric tertiary hospitals in eight regions in mainland China (Shanghai, Hangzhou, Wenzhou, Xi'an, Chongqing, Shenzhen, Shandong, and Kaifeng).

Patient inclusion and exclusion criteria

Inclusion criteria: 1) age less than 5 years; 2) compatible with PM diagnosis criteria. Exclusion criteria: 1) patients with known primary immunodeficiency (including humoral immunity disorders, T-cell and B-cell disorders, phagocytic disorders, and complement disorders) or known secondary immunodeficiency (including human immunodeficiency virus infection, nephrotic syndrome, diabetes, etc); 2) patients had no cranial computed tomography (CT) and magnetic resonance imaging (MRI) results. The diagnostic criteria of PM were as follows: 1) clinical signs and symptoms (bulging fontanelles, stiff or painful neck, vomiting, headache, persistent or recurrent fever, change in mental state, seizures, or focal neurologic signs) that comply with meningitis; 2) the results of CSF examination were abnormal (the white blood cell [WBC] count in CSF was more than 10×10^6/L, in which the neutrophil should be dominant, or the glucose level in CSF was less than 2.78 mmol/L, or the protein level in CSF was more than 0.45 g/L; 3) positive blood culture for *S. pneumoniae* with positive DNA testing of *S. pneumoniae* in CSF, or positive CSF culture for *S. pneumoniae*.

Identification of S. pneumoniae isolates

S. pneumoniae isolate was identified by automatic bacterial identification system (VITEK Compact, France) or Optochin Discs (OXOID, UK) according to the National Guide to Clinical Laboratory Procedures.

Data collection

Case record forms were used to collect data of patients' history, symptoms and signs, laboratory and microbiological findings, clinical course, complications in hospital, vaccination status, treatment, clinical outcome, neurological deficits at discharge, and follow-up visits from the ten hospitals listed in the affiliations. Underlying predisposing factors, including asplenia, history of head trauma or neurosurgery in the past 3 months, anatomical or infectious otorhinolaryngologic disorders, and immunocompromised status, were recorded. Patients with an altered immune status owing to the use of immunosuppressive drugs or splenectomy, diabetes mellitus were considered immunocompromised. Consciousness of the patients was accessed by Glasgow Coma Scale and grouped into normal, decline in consciousness, and coma.

Follow-up

PM patients were followed-up every month in the first year, and every 6 months thereafter. The last

follow-up date was September 30, 2018. OS was calculated from the onset date to the time of death of any cause while SFS was calculated from the onset date to the time of neurological deficits or death of any cause. Assessment was performed by a senior, experienced physician. We called the families to come to hospital for a follow-up visit to complete pediatric exam with a potential neuropsychological assessment. A telephone-based interview was suggested to the families who could not come to hospital. Physical examination, Gesell Development Scale test (<3 years and 10 months), Wechsler Intelligence Scale test (≥3 years and 10 months), and Behavior Questionnaire test (≥2 years) were performed. Neurological sequela was evaluated according to the patients' last results of brain MRI, brainstem auditory evoked potential (BAEP), auditory brainstem response, and visual acuity. Neurological deficits included seizures, hemiparesis, ataxia, hydrocephalus and subdural hydrops or empyema, psychomotor retardation, hearing impairment, and visual impairment. Psychomotor retardation was indicated if gross-motor functions (neck control, sitting, walking, running, etc), fine-motor functions (reaching, grasping, drawing, etc), and activities of daily living (toileting, dressing, eating, writing, etc) were affected. Hearing was considered as impaired when the better ear failed to detect a threshold of 40 dB. Visual impairment was noted if the routine ophthalmic examination results of vision, visual field, fundus oculi, and eye movement were abnormal.

Statistics

Statistical analysis was performed using SPSS 19.0 software (IBM Corporation, Armonk, NY, USA) and GraphPad Prism 6 software (GraphPad Software, Inc., La Jolla, CA, USA). Data were presented as count (%), or median (interquartile range [IQR]). X-title software was used to obtain the best optimal cut-off values of the continuous variables based on prognosis. Chi-squared test and logistic regression analysis were used to investigate the associations of clinical characteristics and laboratory parameters with complications. Kaplan-Meier curves with logrank test and Cox's proportional hazard regression were applied to assess the associations of clinical characteristics and laboratory parameters with prognosis. *P*-value <0.05 was considered significant.

Results

Baseline clinical characteristics

Data from one hundred and sixty-one pediatric patients diagnosed with PM were collected from ten pediatric

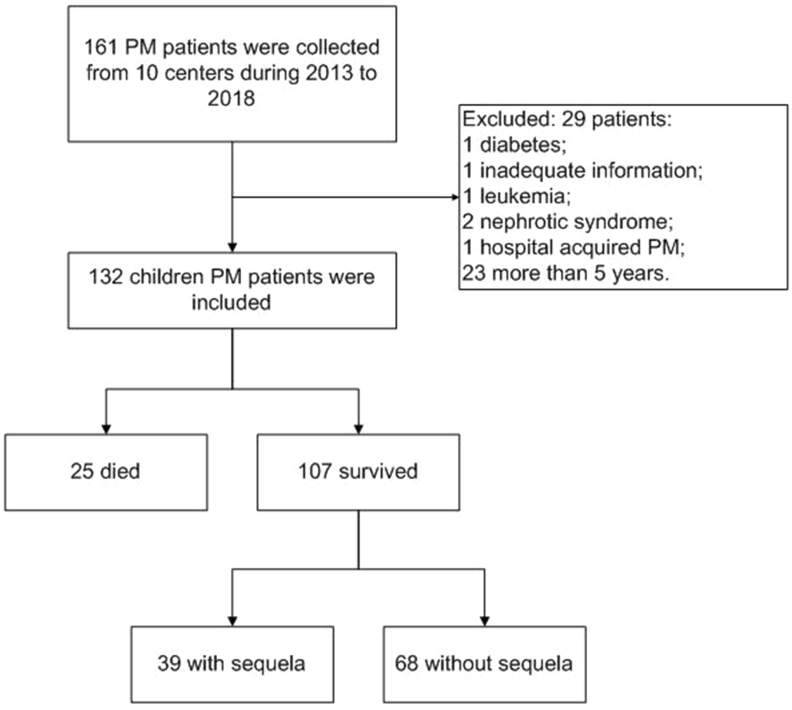

Figure 1 Flowchart of pediatric pneumococcal meningitis (PM) patients' inclusion.

Table 1 Clinical baseline characteristics, laboratory findings, and neurological sequelae of patients with PM

Characteristic	Cases n (%)	Characteristic	Cases n (%)
Total	132(100)		
Sex		**Neurological findings on admission**	
Male	88(66.7)	Triad syndrome	22(16.7)
Female	44(33.3)	Abnormal mental status	46(34.8)
Age		Coma	20(15.2)
Median age (IQR, months)	13(28)	Convulsions on admission	49(37.1)
≤28 months	94(71.2)	**Laboratory findings**	
>28 months	38(28.8)	Positive CSF culture	76(57.6)
Hospital stay		Positive blood culture	31(23.5)
Median time (IQR, days)	22(18)	Positive CSF and blood culture	25(18.9)
Symptoms and signs on admission		WBCs in blood (median, IQR, $\times10^9$/L)	14.5(14.7)
Headache	33(25.0)	Neutrophil proportion in blood (median, IQR, %)	78.5(17.5)
Nausea	80(60.6)	C-Reactive Protein (median, IQR, mg/L)	95.8(111.1)
Neck stiffness	68(51.5)	WBCs in CSF (median, IQR, $\times10^6$/L)	400.0(1756.0)
Bulging fontanelles	27(20.5)	Neutrophil proportion in CSF (median, IQR, %)	80.0(12.8)
Fever	129(97.7)	Protein in CSF (median, IQR, g/L)	1.4 (2.6)
Septic shock	7(5.3)	Glucose in CSF (median, IQR, mmol/L)	1.1 (1.9)
Mechanical ventilation	17(11.4)	**Focal neurological deficits n=107**	39(29.5)
Multiple organ failure	5(3.8)	Hypophrenia or behavioral deficits	18(13.6)
Respiratory failure	9(6.8)	Aphasia	17(12.9)
Predisposing factors[a] n=34	34(25.8)	Dyskinesia	13(9.8)
Recent or remote cerebral trauma	11(8.3)	Hearing impairment	12(9.1)
CSF leakage	13(9.8)	Hydrocephalus	8(6.1)
Previous history of meningitis	6(4.5)	Hemiparesis	8(6.1)
Intracranial structure malformation	5(3.8)	Cranial nerve palsies	5(3.8)
Previous intracranial surgery[b]	4(3.0)	Secondary epilepsy	4(3.0)
Craniotomy	4(3.0)	Quadriplegia	3(2.3)
Concomitant diseases n=84	84(63.6)	Subdural effusion or abscess	2(1.5)
Pneumonia	49(37.1)	Visual impairment	2(1.5)
Sinusitis	22(16.7)	Cerebellar ataxia	1(0.8)
Mastoiditis	24(18.2)	Hypothalamus ataxia	1(0.8)
Otitis	5(3.8)		
Ear or intracranial abnormalities	8(6.1)		

Notes: [a]Predisposing diseases were defined as previous head trauma, history of intracranial surgery, dura disruption, ear or intracranial abnormalities etc. [b]Intracranial surgery (ventriculostomy, cochlear implantation, ventriculoperitoneal shunt, removal of lateral ventricular reservoir sac, cranioplasty, etc.)
Abbreviations: PM, pneumococcal meningitis; IQR, interquartile range; CSF, cerebrospinal fluid; WBC, white blood cell.

tertiary hospitals across China. Twenty-nine patients were excluded due to primary or secondary immunodeficiency, or age more than 5 years and 132 patients were finally included (Figure 1). As shown in Table 1, of the 132 patients, 88 were male and 44 were female. The median age of the patients was 13 months. Lumbar puncture was performed in all patients. Seventy-sixcases had a positive CSF culture for *S. pneumoniae*, 31 cases had a positive blood culture for *S. pneumoniae* with a positive DNA testing of *S. pneumoniae* in CSF, and 25 cases had both positive CSF culture and positive blood culture for *S. pneumoniae*. All patients had signs of meningitis.

An amount of 25.8% (34/132) of patients had predisposing factors for PM including cerebral trauma in eleven (8.3%), CSF leakage in 13 (9.8%), history of meningitis (ie, the patient had meningitis previously) in six (4.5%), intracranial structure malformation in five (3.8%), history of intracranial surgery in four (3.0%), and craniotomy in four (3.0%) (Table 1). Eighty-four PM patients were

combined with other concomitant diseases including pneumoniae, mastoiditis, sinusitis, otitis, and ear or intracranial abnormalities. Fever and vomiting were the most frequent symptoms and signs on admission (97.7% and 60.6%, respectively). The consciousness status was altered in 46 patients on admission, of which 20 (15.2%) were in a coma.

Laboratory examination results were collected from medical records before or at admission. The medians of WBC counts, protein level in CSF, and glucose level in CSF were 14.5×10^9/L (IQR: 14.7×10^9/L), 1.4 g/L (IQR: 2.6 g/L), and 1.1 mmol/L (IQR: 1.9 mmol/L), respectively.

Complications and follow-up

PM complications were found in 53.8% (71/132) of patients by cranial CT and MRI (Table 2). Subdural effusion, sinusitis or otitis, cerebritis, cerebral edema, hydrocephalus, intracranial hemorrhage, and empyema or abscess were the most common abnormalities and present in 47 (35.6%), 35 (26.5%), 29 (22.0%), 22 (16.7%), 17 (12.9%), 15 (11.4%), and 12 (9.1%) patients, respectively. Forty-one patients were associated with more than one abnormality. Twenty-five patients (18.9%) died – all during hospitalization. Nine died within 1 week and 16 patients died 1–4 weeks after admission. The predefined neurological sequelae were evaluated in the 107 survivors during follow-up and identified in 39 patients. Hypophrenia or behavioral deficits, aphasia, dyskinesia, hearing impairment, and hydrocephalus were common focal neurological sequelae and present in 18 (13.6%), 17 (12.9%), 13 (9.8%), 12 (9.1%), and 8 (6.1%) patients of the 107 survivors, respectively (Table 1).

Table 2 Complications of 132 pediatric pneumococcal meningitis patients on admission and during hospitalization examined by cranial computed tomography (CT) or magnetic resonance imaging (MRI) for

Characteristic	Patients n (%)[a]
Total number of abnormalities[b]	71(53.8)
Subdural effusion	47(35.6)
Sinusitis or otitis	35(26.5)
Cerebritis	29(22.0)
Cerebral edema	22(16.7)
Hydrocephalus	17(12.9)
Intracranial hemorrhage	15(11.4)
Empyema or abscess	12(9.1)
Cerebral atrophy	7(5.3)
Skull fracture	7(5.3)
Cerebral hernia	5(3.8)
Brain infarction	4(3.0)
Arachnoid cyst	3(2.3)
Other abnormalities[c]	7(5.3)

Notes: [a]Data are numbers (%). Percentages are calculated per number of episodes with cranial CT or MRI undertaken. [b]Numbers do not add up to totals because of the presence of multiple abnormalities in several patients. [c]Middle ear malformation in three, pneumocephalus in two, meningioma in one, and cerebral vascular malformation in one.

Associations of clinical findings and laboratory parameters with complications

Chi-squared test was used to investigate the associations of clinical findings and laboratory parameters with complications and the results suggested that age less than 28 months, visual impairment, convulsions on admission, lower WBCs in blood, and predisposing factors were associated with complications in pediatric PM patients (Table 3). Further multivariate logistic regression analysis revealed that age less than 28 months (aOR=2.654, 95% CI=1.067–6.600, P=0.036) and lower WBCs in blood (aOR=3.169, 95%CI=1.395–7.202, P=0.006) were independent predictive factors for complications in pediatric PM patients (Table 4).

Associations of clinical findings and laboratory parameters with accumulating OS

Kaplan-Meier plot curves and univariate Cox's proportional hazard regression were used to investigate the associations of clinical findings and laboratory parameters with accumulating OS and the results suggested that female sex, age less than 28 months (Figure 2A), coma (Figure 2B), convulsions on admission, respiratory failure, multiple organ dysfunction syndrome (MODS) (omit RF), ventilation, septic shock, non-adjuvant steroid therapy (Figure 2C), and higher protein level in CSF were associated with shorter OS in pediatric PM patients (Table 5). Further multivariate Cox's proportional hazard regression revealed that age less than 28 months (aHR=6.479, 95%CI=1.153–36.404, P=0.034), coma (aHR=9.808, 95%CI=2.802–34.323, P=0.000), and non-adjuvant steroid therapy (aHR=4.768 95% CI=1.946–11.678, P=0.001) were independent prognostic factors for poor OS in pediatric PM patients (Table 5).

Table 3 Associations of the clinical features with complications in pediatric PM patients analyzed by chi-squared test

Parameters	Subgroups	Complications		Chi-squared	*P*-value
		NO	YES		
Sex	Male	21	23	0.061	0.805
	Female	40	48		
Age	≤28 months)	34	60	13.247	**0.000**
	>28 months	27	11		
Duration of disease	≤4 days	37	48	0.691	0.406
	>4 days	24	23		
Consciousness state	Normal	44	42	2.488	0.288
	Decline in consciousness	10	16		
	Coma	7	13		
Convulsions on admission	NO	46	36	8.511	**0.004**
	YES	15	35		
Respiratory failure	NO	56	67	0.339	0.560
	YES	5	4		
MODS	NO	59	68	0.081	0.776
	YES	2	3		
Mechanical ventilation	NO	56	61	1.129	0.288
	YES	5	10		
Septic shock on admission	NO	58	67	0.033	0.855
	YES	3	4		
Adjuvant steroid therapy	NO	16	18	0.013	0.909
	YES	45	53		
Antibiotics treatment	Early	15	12	1.192	0.275
	Late	46	59		
WBCs in blood	High	48	36	11.104	**0.001**
	Low	13	35		
WBCs in CSF	High	15	18	0.010	0.920
	Low	40	50		
Glucose in CSF	High	24	28	0.000	0.991
	Low	37	43		
Protein in CSF	Low	28	38	1.515	0.218
	High	29	25		
Predisposing factors	NO	22	12	6.301	**0.012**
	YES	39	59		
Concomitant disease	NO	38	46	0.030	0.863
	YES	22	25		

Note: Bold, indicates $P<0.05$.
Abbreviations: PM, pneumococcal meningitis; MODS, multiple organ dysfunction syndrome; CSF, cerebrospinal fluid; WBC, white blood cell.

Table 4 Associations of the clinical features with complications in pediatric PM patients analyzed by multivariate logistic regression

Parameters	*P*-value	OR	95%CI	
Age (≤28 months vs >28 months)	0.036	2.654	1.067	6.600
Convulsions on admission (YES vs NO)	0.156	1.823	0.795	4.181
WBCs in blood (low vs high)	0.006	3.169	1.395	7.202
Predisposing factors (YES vs NO)	0.150	1.946	0.785	4.825

Note: Bold, indicates $P<0.05$.
Abbreviations: PM, pneumococcal meningitis; WBC, white blood cell.

Correlation of clinical findings and laboratory parameters with accumulating SFS

Associations of clinical findings and laboratory parameters with accumulating SFS were also explored. The Kaplan-Meier curves and univariate Cox's proportional hazard regression suggested that coma (Figure 3A), convulsions on admission, respiratory failure, MODS (omit RF), mechanical ventilation, septic shock on admission (Figure 3B), non-adjuvant steroid therapy,

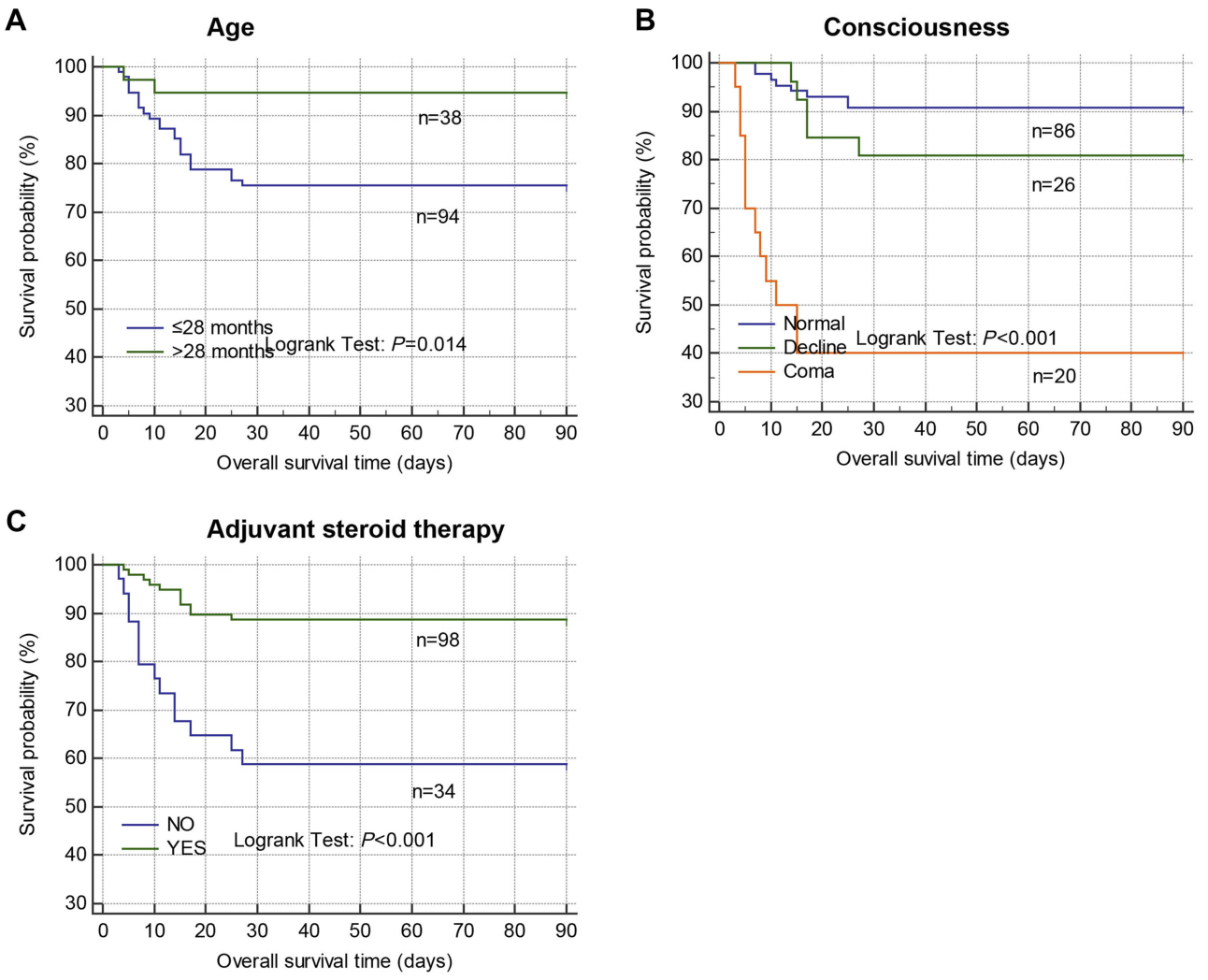

Figure 2 Associations of clinical characteristics with accumulating overall survival in pediatric pneumococcal meningitis (PM) patients were analyzed by Kaplan-Meier plot curves and logrank test. (**A**) age; (**B**) consciousness; (**C**) steroid therapy.

and lower glucose level in CSF (Figure 3C) were associated with shorter SFS (Table 6). After adjusting the confounding factors, coma (aHR=5.841, 95% CI=2.652–12.864, *P*=0.000), septic shock on admission (aHR=2.949, 95%CI=1.049–8.290, *P*=0.040), and lower glucose level in CSF (aHR=2.523, 95%CI=1.336–4.765, *P*=0.004) were found to be independent prognostic factors for unfavorable SFS in multivariate analyses (Table 6).

Discussion

In the present multicenter study, we included 132 pediatric patients and revealed that the overall mortality of these patients was 18.9% and the rate of focal neurological sequelae 36.4%, which were higher than that observed in US or European populations.[5–8,17,25,27,28] A meta-analysis in 1993, including mainly US and European cohorts, revealed a mortality rate of 4.8%–8.1% and a neurological handicap rate of 16%–26% in pediatric PM patients.[29] Another meta-analysis in 2014, performed in Latin American and Caribbean populations, suggested that the mortality rate of pediatric PM patents was 8.3%.[30] In developing countries and regions such as sub-Saharan Africa, the mortality of PM patients has been reported to be as high as 73%.[7,9–13] The mortality of pediatric PM patients in China was higher than US or European cohorts but lower than African cohorts. The higher mortality and neurological sequelae rates emphasized the need to identify early prognostic factors for pediatric PM patients.

Of the 132 pediatric PM patients in the study, meningitis-associated intracranial complications were found in

Table 5 Associations of the clinical features with accumulating OS in pediatric PM patients analyzed by Cox's proportional hazard regression

Parameters	Univariate analysis				Multivariate analysis			
	P-value	HR	95%CI		*P*-value	HR	95%CI	
Sex (female vs male)	**0.010**	2.812	1.276	6.199	0.189	1.774	0.754	4.171
Age (≤28 months vs >28 months)	**0.028**	5.032	1.186	21.346	**0.034**	6.479	1.153	36.404
Duration of disease (>4 days vs ≤4 days)	0.189	1.692	0.772	3.709				
Complications (YES vs NO)	0.473	0.750	0.342	1.645				
Consciousness state	**0.000**				**0.002**			
Normal		Ref				Ref.		
Decline in consciousness	0.202	2.071	0.678	6.332	0.079	2.916	0.882	9.643
Coma	**0.000**	10.641	4.321	26.201	**0.000**	9.808	2.802	34.323
Convulsions on admission (YES vs NO)	**0.043**	2.258	1.025	4.976	0.205	0.442	0.125	1.560
Respiratory failure (YES vs NO)	**0.000**	8.988	3.705	21.806	0.396	1.903	0.431	8.401
MODS (YES vs NO)	**0.001**	6.363	2.170	18.659	0.326	1.808	0.555	5.888
Mechanical ventilation (YES vs NO)	**0.000**	5.781	2.547	13.124	0.194	2.572	0.619	10.683
Septic shock on admission (YES vs NO)	**0.000**	14.465	5.519	37.914	0.053	3.927	0.983	15.693
Adjuvant steroid therapy (NO vs YES)	**0.000**	4.491	2.036	9.906	**0.001**	4.768	1.946	11.678
Antibiotics treatment (late vs early)	0.531	1.408	0.483	4.102				
WBCs in blood (low vs high)	0.174	1.723	0.786	3.776				
WBCs in CSF (low vs high)	0.144	2.054	0.782	5.399				
Glucose in CSF (low vs high)	0.147	1.990	0.785	5.049				
Protein in CSF (high vs low)	**0.034**	2.536	1.074	5.984	0.953	1.039	0.292	3.693
Concomitant disease (YES vs NO)	0.065	2.512	0.943	6.696				
Predisposing factors (YES vs NO)	0.780	0.883	0.369	2.114				

Note: Bold, indicates $P<0.05$.
Abbreviations: OS, overall survivalPM, pneumococcal meningitis; MODS, multiple organ dysfunction syndrome; CSF, cerebrospinal fluid; WBC, white blood cell.

53.8% patients by cranial CT or MRI. The most common intracranial complications were subdural effusion, cerebritis, cerebral edema, and hydrocephalus. The prevalence of cerebritis and hydrocephalus in our study was higher than adult PM patients in previous study of.[31] The prevalence of concomitant diseases was 63.6% in our study and was similar to the results of previous reports.[31–34]

After multivariate analyses of the prognostic factors in predicting complications, OS, and SFS outcomes in pediatric PM patients, we identified that age less than 28 months was associated with complications (aOR=2.654, 95%CI=1.067–6.600, P=0.036) and short OS (aHR=6.479, 95%CI=1.153–36.404, P=0.034), coma on admission was associated with short OS (aHR=9.808, 95%CI=2.802–34.323, P=0.000) and SFS (aHR=5.841, 95%CI=2.652–12.864, P=0.000), non-adjuvant steroid therapy was associated with short OS (aHR=4.768 95%CI=1.946–11.678, P=0.001), and septic shock on admission was associated with poor SFS (aHR=2.949, 95%CI=1.049–8.290, P=0.040). Our results were similar to previous reports.[16,17,25,26] According to previous evidence, the CSF of PM patients usually shows aberrant WBC count, protein level, and glucose level, thus we also analyzed the prognostic value of WBCs in blood or CSF, protein in CSF, and glucose in CSF to predict complications, OS, and SFS in pediatric PM patients. Our result suggested that lower WBCs in blood was an independent predictive factor of complications and lower glucose level in CSF was an independent prognostic factor of poor SFS. Leukopenia is reflective of severe sepsis, and lower peripheral blood and CSF WBC counts may indicate inadequacy of the immune response. Chao et al also found an association between lower WBCs in CSF and higher mortality in PM.[19] Lower glucose levels in the CSF is correlated with increased inflammation and cytokine levels[35] and the inflammatory response is implicated in the pathogenesis of PM and associated brain injury and neuronal death, via releasing potentially cytotoxic agents such as ROS and proteolytic enzymes by leucocytes recruited during the inflammatory response.[36] A lower glucose level in CSF can indicate increased central nervous system inflammation, which is expected to result in a higher risk of neurological sequelae and poor SFS in PM

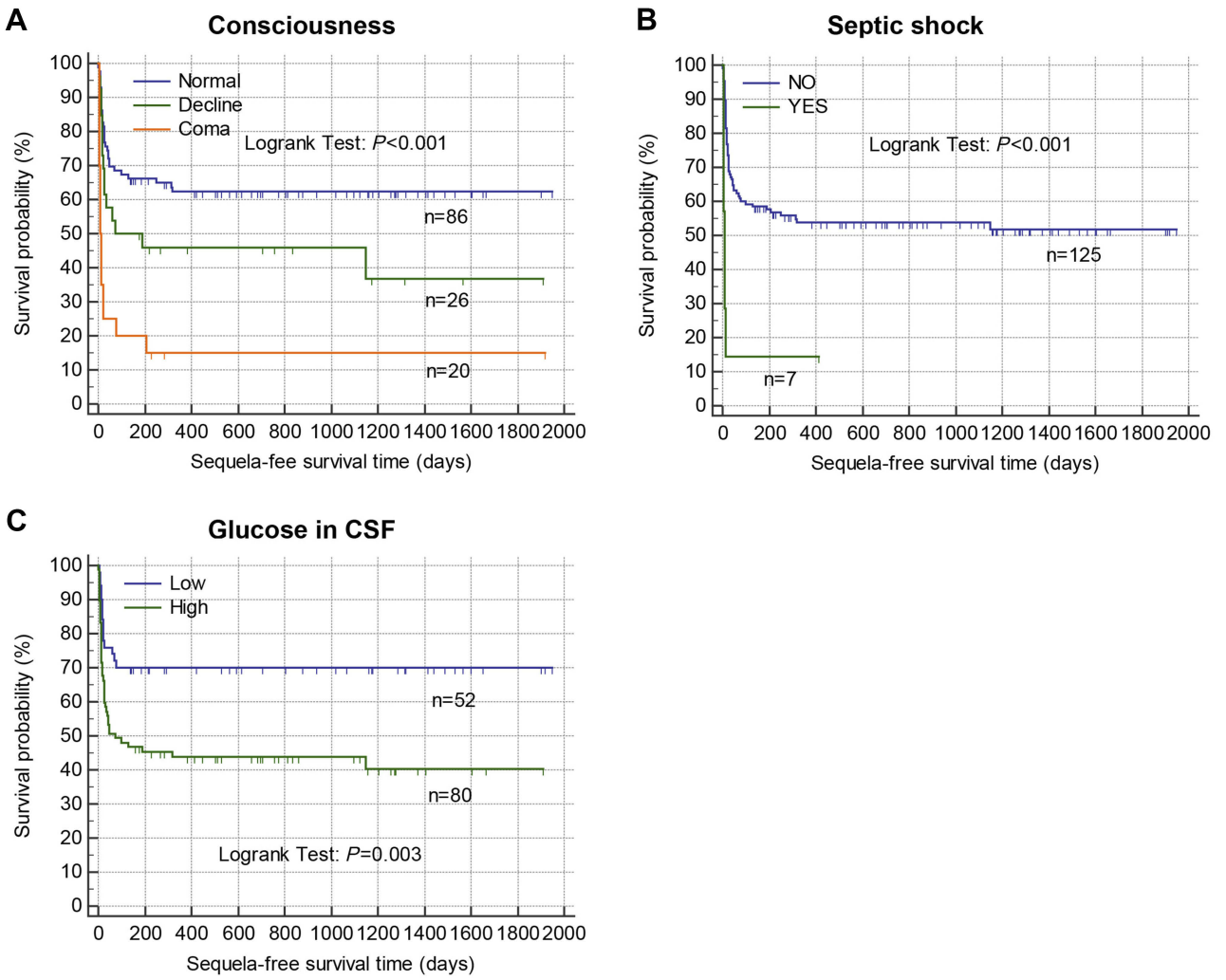

Figure 3 Associations of clinical characteristics and laboratory parameters with accumulating sequelae-free survival in pediatric pneumococcal meningitis (PM) patients were analyzed by Kaplan-Meier plot curves and logrank test. (**A**) Consciousness; (**B**) septic shock; (**C**) glucose in cerebrospinal fluid (CSF).

patients. High protein levels in CSF are related to more severe inflammatory reactions and immune responses during bacterial meningitis,[37,38] and may also be a predictor of later poor outcomes in PM patients, although we only observed an association between protein level in CSF and OS in univariate analysis.

This study is the most comprehensive nationwide, multi-centric study on pediatric PM in mainland China up to date. However, some limitations still existed in our study. Firstly, information on capsular serotyping of the pediatric PM patients in our retrospective study was not available and the associations of serotype distribution with clinical outcomes of the patients were not clear. Secondly, although pneumococcal vaccines have been licensed in mainland China, none of the patients in our study received pneumococcal vaccination, which might also be associated with prognosis in PM patients.

Conclusion

Our study showed that PM is a disease with high mortality and neurological sequelae in pediatric patients, and complications during the clinical course occur frequently. In pediatric PM patients, age less than 28 months and lower WBCs in blood were independent predictive factors for complications; age less than 28 months, coma, and non-adjuvant steroid therapy were independent prognostic factors for poor OS; and coma, septic shock on admission, and lower glucose level in CSF were independent prognostic factors for poor SFS.

Table 6 Associations of the clinical features with accumulating SFS analyzed by Cox's proportional hazard regression

Parameters	Univariate analysis				Multivariate analysis			
	P-value	HR	95%CI		*P*-value	HR	95%CI	
Sex (female vs male)	0.521	1.184	0.706	1.985				
Age (≤28 months vs >28 months)	0.181	1.485	0.832	2.650				
Duration of disease (>4 days vs ≤4 days)	0.064	1.593	0.973	2.609				
Complications (YES vs NO)	0.457	1.208	0.735	1.984				
Consciousness state	**0.000**				**0.000**			
Normal		Ref				Ref		
Decline in consciousness	0.079	1.735	0.939	3.207	0.080	1.789	0.932	3.434
Coma	**0.000**	4.971	2.732	9.046	**0.000**	5.841	2.652	12.864
Convulsions on admission (YES vs NO)	**0.050**	1.638	1.001	2.683	0.915	1.034	0.559	1.912
Respiratory failure (YES vs NO)	**0.000**	4.337	2.037	9.233	0.566	1.413	0.433	4.607
MODS (YES vs NO)	**0.003**	4.041	1.591	10.260	0.209	1.868	0.704	4.954
Mechanical ventilation (YES vs NO)	**0.008**	2.404	1.252	4.618	0.783	1.148	0.430	3.060
Septic shock on admission (YES vs NO)	**0.000**	5.446	2.307	12.858	**0.040**	2.949	1.049	8.290
Adjuvant steroid therapy (NO vs YES)	**0.030**	1.785	1.058	3.011	0.055	1.771	0.989	3.173
Antibiotics treatment (late vs early)	0.425	0.794	0.450	1.399				
WBCs in blood (low vs high)	0.059	1.610	0.982	2.641				
WBCs in CSF (low vs high)	0.062	1.695	0.974	2.950				
Glucose in CSF (low vs high)	**0.004**	2.345	1.304	4.217	**0.004**	2.523	1.336	4.765
Protein in CSF (high vs low)	0.318	1.301	0.777	2.178				
Concomitant disease (YES vs NO)	0.848	1.051	0.633	1.744				
Predisposing factors (YES vs NO)	0.990	0.997	0.566	1.755				

Note: Bold, indicates *P*<0.05.

Abbreviations: SFS, sequelae-free survival; PM, pneumococcal meningitis; MODS, multiple organ dysfunction syndrome; CSF, cerebrospinal fluid; WBC, white blood cell.

Ethics

The present study was approved by the Ethics Committee of the Children's Hospital of Zhejiang University School of Medicine. Each PM patient was anonymous in the study and patient/parental consent requirement was waived due to the anonymized data.

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Author contributions

Caiyun Wang, Hongmei Xu, Jikui Deng, Hui Yu, Yiping Chen, Shifu Wang, Weichun Huang, Jianhua Hao, Chun Wang, Huiling Deng, and Yinghu Chen designed the study. Caiyun Wang and Yinghu Chen drafted the manuscript. All authors contributed to data analysis, drafting and revising the article. All authors

gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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