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Jumonji Domain-containing 3 (Jmjd3) Promoted Inflammation by PHF20 Ubiquitination to Induce p65 in Paediatric Patients with Septicemia

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KEYWORDS Jumonji Domain-containing 3. Plant Homeodomain Finger Protein 20. p65. Paediatric Sepsis. Ubiquitination

ABSTRACT Inflammation septicemia is a systemic infectious disease, which is seriously harmful to the health of the patient, caused by bacteria. This study aimed to investigate the function and possible mechanism of Jumonji domain-containing 3 (Jmjd3) in a model of paediatric patients with septicemia. The subjects included 12 paediatric patients with septicemia and 12 normal healthy volunteers at our hospital.Infant (2 weeks old) C57BL/6 mice were received with lipopolysaccharide (LPS).THP-1 cell was induced with LPS. The serum expression of Jmjd3 mRNA level in paediatric patients with septicemia was up-regulated. Jmjd3 protein and mRNA expression in lung tissue were induced in mice with septicemia. Jmjd3 promoted inflammation *in vitro model* of septicemia. Jmjd3 promoted septicemia and inflammation in the mice model. Jmjd3 induced p65 in paediatric mice with septicemia by plant homeodomain finger protein 20 (PHF20) Ubiquitination. Taken together, the findings demonstrate Jmjd3 promoted inflammation by PHF20 Ubiquitination to induce p65 in paediatric patients with septicemia. The researchers identified that Jmjd3 could hopefully become a therapeutic strategy for paediatric sepsis.

INTRODUCTION

As one of the common clinical diseases, suppurative meningitis is a high incidence stage in the neonatal period (Ashfaq et al. 2021). After the onset of the disease, the intelligence and hearing of the child will be affected to some extent. If the treatment is not timely, it is easy to cause epilepsy, hydrocephalus and other sequelae, which seriously threatens the health of the child (Ashfaq et al. 2021). In order to ensure the life safety of newborns, clinical attention should be paid to children with low body weight, less than 7 days old, premature infants, premature rupture of membranes, staphylococcus aureus and Escherichia coli as the cause of septicemia, and the occurrence of suppurative meningitis should be effectively prevented by closely monitoring the vital signs of children (Driessen et al. 2021).

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Inflammation septicemia is a systemic infectious disease, which is seriously harmful to the health of the patient caused by bacteria invading the host blood and producing multiple toxic products (Ashfaq et al. 2021; Driessen et al. 2021). According to reports, the mortality rate of septicemia in the United States is thirty percent to fifty percent, and 750,000 people are septicemia each year, 225,000 of them are dead, and the incidence rate of septicemia is rising at the rate of 1.5 percent to 8.0 percent per year (Li et al. 2021a). Because the organs, immune system and stress system of a newborn are incompletely functioning, infection is complicated with multiple organ failure.

Neonatal septicemia is a common disease of newborn babies, with an incidence of 0.1 percent to 1.0 percent of live births and a mortality of 10 percent to 50 percent. A considerable part of survivors have sequelae. At present, blood culture is still the gold standard for the diagnosis of neonatal septicemia (Driessen et al. 2021). If blood culture is detected by radionuclide method, the results can be obtained within 24 to 72 hours. If penicillin and cephalosporin antibiotics are used for a long time, L-type bacteria should be sent for culture (Driessen et al. 2021). It takes 7 to 14 days to obtain the results using hypertonic culture

medium. Both methods bring difficulties to early diagnosis. Scholars at home and abroad are committed to seeking more accurate early diagnostic indicators of sepsis, such as procalcitonin, interleukin, tumor necrosis factor (TNF), CD64, etc., but these experimental parameters are still subject to various limitations in clinical application. The clinical manifestations of neonatal septicemia are not specific, so early diagnosis and treatment are particularly important for children. However, in areas with relatively backward economy and limited medical resources and level, early detection and treatment of neonatal septicemia is extremely difficult (Li et al. 2021a).

NF-κB signalling pathway regulates TNF-α and IL-6 and it is activated in sepsis (Hu et al. 2021). Sepsis can activate NF-κB signalling pathways in the human pulmonary vascular endothelial cells, stimulate inflammatory response and damage vascular endothelial cells (Lasola et al. 2021). When the NF-κB signalling pathway is activated, p65 protein is separated and enters the nucleus to play the role of transcription factor (Matsumoto et al. 2021; Zhang et al. 2021; Li et al. 2021; Liu et al 2022a). Therefore, detecting the expression of p65 in the nucleus can reflect NF-κB signal pathway activation (Mohamed et al. 2021; Liu et al. 2022a).

PHF20 protein contains multiple functional domains, which was initially found as an autoantibody in patients with glioblastoma. Its second Tudor region can recognise and bind p53 (Liu et al. 2021; Long et al. 2018). After binding, it can stabilise and promote the active transcription of p53 by preventing the ubiquitination of p53 (Ma et al. 2020; Liu and Yu 2022; Wang et al. 2021).

Jmjd3 is a specific demethylase. Inhibition of jmjd3 can increase cell activity and reduce the incidence of apoptosis (Davis et al. 2021). Macrophages are important immune cells in vivo, and epigenetic modification has an important impact on their biological functions (Li et al. 2021b). Jmjd3 is an important epigenetic modified enzyme. In recent years, many literatures have reported that jmjd3 is closely related to macrophage polarisation and inflammatory gene expression (Roy et al. 2021; Yang et al. 2021; Liu et al. 2022b).

Objective of the Study

This study investigated the effects of Jmjd3 on paediatric patients with septicemia and its underlying mechanism in vivo and vitro.

MATERIAL AND METHODS

Patients

A total of 12 paediatric patients with septicemia and 12 normal healthy volunteers were obtained from an affiliated hospital of Putian University from January 2019 to May 2020. No patients had received chemotherapy or pre-operative radiotherapy. The written informed consents were obtained from all the subjects and this study was approved by the Ethics Committee of the affiliated hospital of Putian University. Peripheral blood was extracted from veinal blood and serum was collected at 1000 g for 10 minutes. All the serum samples were immediately stored at -80°C and measured Jmjd3 mRNA expression within 1 week.

Mice Experiment

Infant (2 weeks old) C57BL/6 mice were housed in barrier cages under controlled environmental conditions (22-23 °C, 12/12 hours of light/dark cycle, 55% ± 5% humidity). All mice were randomly allocated into the sham group (n = 6), model group (n = 6) or model group (n = 6), model + Jmjd3 group (n = 6). In the model group, C57BL/6 mice were received with LPS (30 mg/kg, i.p.). In the sham group, C57BL/6 mice were received with normal saline. After induction sepsis, the mice recorded a survival rate every day for three days. At three days, all mice were anaesthetised using 50 mg/kg pentobarbital sodium and then sacrificed using cervical spondylectomy.

Quantitative PCR

The total RNA was extracted from serum and cell samples using a TRIZOL reagent (Life Technologies Inc.). Total RNA were transcribed to cDNAs using Prime Script RT reagent kit (Takara, RR037A). qRT-PCR assays were performed using LightCycler® 480 SYBR Mix (Roche, Germany) using LightCycler® 480 real-time PCR system. The expression levels of mRNA were normalised to the β-Actin expression using the $2^{-\Delta\Delta ct}$ method. The reaction conditions were as follows, that is, 95°C for 10 minutes, followed by 40 cycles of 95°C for 30 seconds and 60°C for 60 seconds.RT-qPCR primers are listed as Jmjd3Forward Primer: 5'-

CAATCTTGGATGACCTCTATG-3' and Reverse Primer: 5'-GTTCTTCACCTCGTTCCACTC-3', β-Actin Forward Primer: 5'-TGCTAGGAGCCAGAGCAGTA-3' and 5'-AGTGTGACGTTGACATCCGT-3'.

Microarray Analysis

Total RNA was extracted from serum samples, and the amount of RNA was quantified by use of NanoDrop 1000. Total RNA of each sample was used for reverse transcription using an Invitrogen SuperScript double stranded cDNA synthesis kit. Double-stranded cDNA was executed with a NimbleGen one-colour DNA labelling kit and then executed for array hybridisation using the NimbleGen hybridisation system and washing with the NimbleGen wash buffer kit. Axon GenePix 4000B microarray scanner (Molecular Devices) was used for scanning.

Cell Culture and RNA Interference

THP-1 cell were cultured in RPMI 1640 medium (Gibco, Carlsbad, CA, USA) supplemented with ten percent foetal calf serum (FCS, Gibco, Carlsbad, CA, USA) in a humidified atmosphere of five percent CO2 at 37°C. Plasmids were transfected into PBMCs using Lipofectamine 2000. After 48 hours of transfection, cells were induced with 0.1 mg/ml LPS for 4 hours.

ELISA Kits

The IL-1β (PI301), IL-6 (PI326), INF-γ (PI508) and TNF-α (PT512) levels were performed according to the instructions of the ELISA kit (Beyotime Institute of Biotechnology, China). The absorbance value was quickly read using the microplate reader at a detection wavelength of 450 nm as literature.

Western Blot Analysis

Total protein was extracted from lung samples or cell samples using Radio-Immunoprecipitation Assay (RIPA) and PMSF reagent (Beyotime, Beijing, China). Protein lysates were separated based on their molecular weight on SDS/PAGE gels and transferred onto a Polyvinylidene Fluoride (PVDF, Millipore) membrane. The membrane was blocked with nonfat-milk (5%) for 2 hours at room temperature and incubated with ant-Jmjd3 antibody, anti-PHF20 antibody, anti-p65 antibody and anti-β-actin antibody at 4°C overnight. The first antibodies were removed and the membrane was washed using TBST. The membranes were incubated with the secondary antibody for 2 hours at room temperature. The bound antibodies were detected using enhanced chemiluminescence (ECL) with β-actin used as a control.

Immunofluorescence

Cells were fixed with four percent paraformaldehyde, permeabilised with 0.5 percent Triton X 100 in PBS for 15 minutes at room temperature, and blocked with five percent BSA for 30 minutes at 37°C. Cells were treated with primary antibodies at 4°C overnight, and were then incubated with Cy3-conjugated goat anti-rabbit or goat anti-mouse IgG DyLight 488 conjugated secondary antibodies for 2 hours at 37°C. Nuclei were stained with DAPI and cells were observed under a fluorescent illumination microscope (Olympus IX71, Tokyo, Japan).

Statistical Analysis

Graphad Prism 6 was used for the statistical analysis. All values are expressed as means ± SEM unless specified (repeat n = 3). $P < 0.05$ was considered statistically significant. The differences between groups were analysed using Student's t-test. Multiple groups were obtained by one-way ANOVA.

RESULTS

The Expression of Jmjd3 in Paediatric Patients with Septicemia or Mice with Septicemia

Firstly, the experiment found that the serum expression of Jmjd3 mRNA level in paediatric patients with septicemia were up-regulated, as compared with normal healthy volunteers (0.596±0.241 vs 9.044±5.084, Fig. 1A). Additionally, serum mRNA of Jmjd3 was positive correlation with serum IL-1β levels in paediatric patients with septicemia ($Y = 0.5497^{*}X + 1.951$, Fig. 1B) and the receiver operating characteristic (ROC) curve was constructed to assess diagnostic value of Jmjd3 level (AUC=0.9583, Fig. 1C). Among the mice with sep-

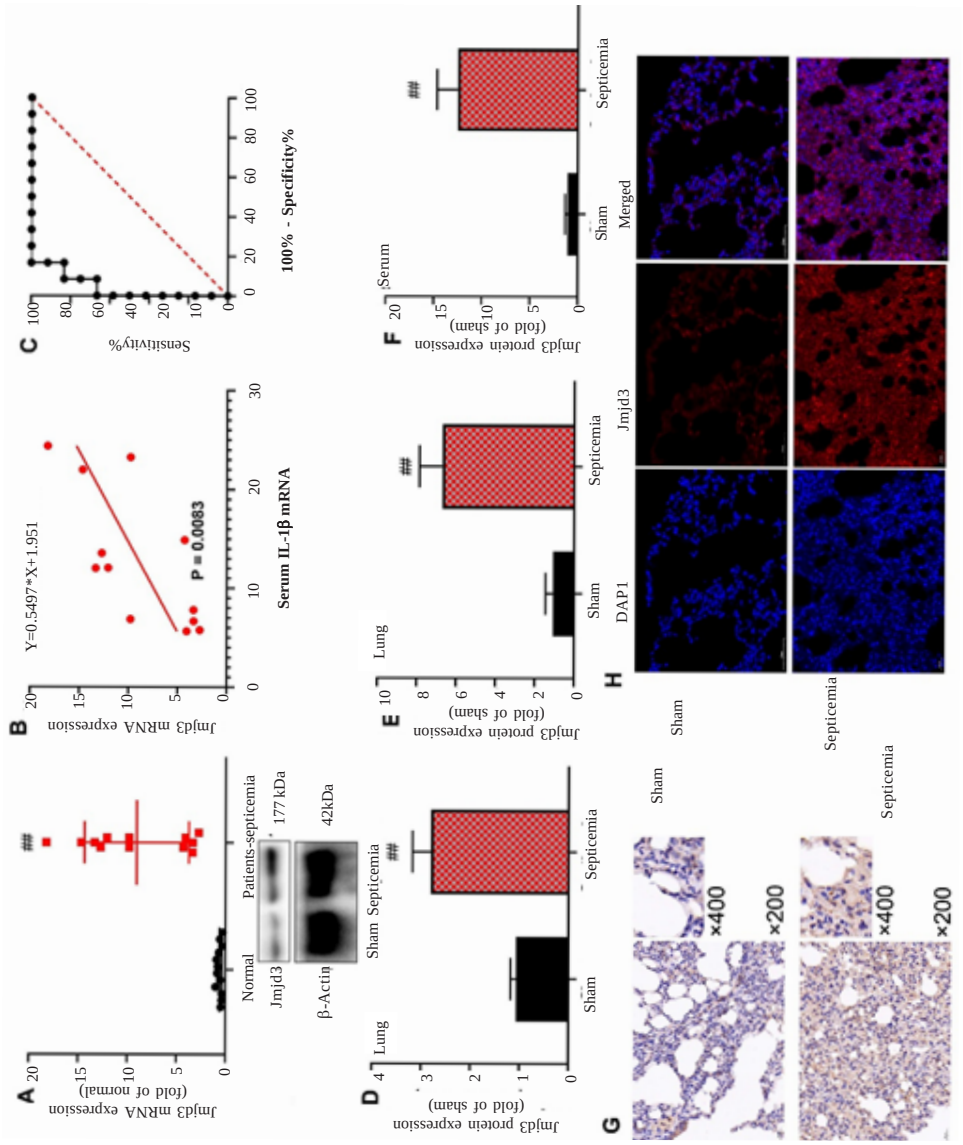

Fig. 1. The expression of Jmjd3 in pediatric patients with septicemia or mice with septicemia
Jmjd3 mRNA expression (A), serum mRNA of Jmjd3 was positive correlation with serum IL-1β levels and ROC (B and C) in pediatric patients with septicemia; Jmjd3 protein (D) and mRNA expression (E) in lung tissue, Jmjd3 mRNA expression (F) in serum, Immunofluorescence for Jmjd3 expression (G) and immunohistochemical for Jmjd3 expression (H) in mice with septicemia
Normal, normal volunteers group; Patients-septicemia, Patients with septicemia; Sham, sham control group; septicemia, mice with septicemia ##p<0.01 compared with normal volunteers group or sham control group

ticemia, Jmjd3 protein (1.064±0.114 vs 2.806±0.373) and mRNA expression (1.072±0.385 vs 6.709±1.158) in lung tissue were induced (Fig. 1D-1E). Meanwhile, serum Jmjd3 mRNA expression (1.057±0.258 vs 14.574±1.685) in mice with septicemia were also induced (Fig. 1F). Immunofluorescence and immunohistochemical studies showed that Jmjd3 expression was increased in lung tissue of mice with septicemia (Fig. 1G-1H).

Jmjd3 Promoted Inflammation In Vitro Model of Septicemia

Furthermore, the researchers investigated the function of Jmjd3 on inflammation in vitro model of septicemia. The Jmjd3 mRNA expression (1.120± 0.562 vs 7.865±2.407) was increased in over-expression of Jmjd3 group and Jmjd3 mRNA expression (1.024±0.211 vs 0.810±0.075 vs 0.426±0.159 vs 0.271±0.043) was down-regulated in si-Jmjd3 group (Fig. 2A). Over-expression of Jmjd3 increased IL-1β (432.5±31.42 vs 930±84.18), IL-6 (151.33±32.67 vs 230±19.25), INF-γ (50±5.10 vs 127± 8.29 pg/ml) and TNF-α (608.33±44.97 vs 1321.67± 147.04 pg/ml) levels in vitro model of septocemia (Fig. 2B-2E). Down-regulation of Jmjd3 reduced IL-1β (51±3.56 vs 16.67±1.70 pg/ml), IL-6 (392.5± 33.73 vs 190±36.91 pg/ml), INF-γ (78.67±6.55 vs 22.33±2.87 pg/ml) and TNF-α (605±230.36 vs 200±45.46 pg/ml) levels in vitro model of septicemia (Fig. 2-2I).

Jmjd3 Promoted Septicemia and Inflammation in Mice Model

The researchers further examined the function of Jmjd3 in the mice model of septicemia. Human Jmjd3 recombinant protein reduced survival rate, increased W/D rate (6.63±0.416 vs 8.433±0.15) and lung injury score (5.5±0.26 vs 6.67±0.25), promoted lung injury, neutrophils (1433333.33±57735.03 vs 2166666.67±76376.26) and protein concentrations of BAL (1.10±0.07 vs 1.74±0.07), and inhibited lung injury, lung bacterial CFU (1372±101.23 vs 2346.67±87.67), BAL fluid haemoglobin (Hgb) concentration (0.20±0.02 vs 0.47±0.09) and BAL fluid OD540 (1.38±0.15 vs 2.47±0.22), and increased platelets (254±28.93 vs 140.33±17.56) in BAL of mice with sepsis (Fig. 3A-3J). Human Jmjd3 recombinant protein promoted the serum IL-1β (377.5±36.91 vs 1142.5±81.55 pg/ml), IL-6 (161.33±10.50 vs 327.33±37.03 pg/ml), INF-γ (58±2.45 vs 163.33±22.53 pg/ml) and TNF-α (575±43.20 vs 1161.67±281.94 pg/ml) levels in mice with sepsis (Fig. 3K-3N).

Jmjd3 Induce p65 in Paediatric with Septicemia by PHF20 Ubiquitination

To understand the mechanism of Jmjd3 in pediatric with septicemia, microarray analysis was performed to screen the gene expression (Fig. 4A). Human Jmjd3 recombinant protein induced PHF20 (1.139±0.136 vs 3.028±0.368) and p65 (0.768±0.241 vs 2.845±0.325) protein expressions in mice with sepsis (Fig. 4B-4C). Immunofluorescence showed that over-expression of Jmjd3 increased the expression of Jmjd3 and PHF20 in vitro model (Fig. 5A). Over-expression of Jmjd3 induced Jmjd3 (1.210±0.209 vs 3.087±0.502), PHF20 (1.143±0.102 vs 2.512±0.442) and p65 (0.937±0.045 vs 3.337± 0.466) protein expressions in vitro model (Fig. 5B-5D). Down-regulation of Jmjd3 suppressed Jmjd3 (1.100±0.073 vs 0.317±0.046), PHF20 (1.243±0.202 vs 0.416±0.077) and p65 (1.053±0.133 vs 0.391± 0.127) protein expressions in vitro model (Fig. 5E-5G). The researchers confirmed the association between Jmjd3 and PHF20 proteins by Co-IP (Fig. 5H). Over-expression of Jmjd3 reduced PHF20 ubiquitination and down-regulation of Jmjd3 increased PHF20 ubiquitination in vitro model (Fig. 5I).

Next, si-PHF20 suppressed PHF20 (1.219±0.216 vs 3.167±0.346 vs 1.362±0.138) and p65 (1.07±0.115 vs 3.339±0.263 vs 1.502±0.167) protein expressions in vitro model following Jmjd3 up-regulation, comparing with Jmjd3 up-regulation (Fig. 6A-6B). PHF20 over-expression also reversed the effects of Jmjd3 down-regulation on PHF20(1.224±0.178 vs 0.356±0.06 vs 0.817±0.067) and p65 (0.953±0.036 vs 0.335±0.076 vs 0.781±0.023) protein expression (Fig. 6C-6D). Si-PHF20 could reduce IL-1β (455±43.45 vs 1130±28.94vs 622.5±67.18 pg/ml), IL-6 (174.67± 13.30 vs 356.67±33.36 vs 214±20.07 pg/ml), INF-β (60±5.10 vs 179.33±10.66 vs 90±2.16 pg/ml) and TNF-α (598.33±122.30 vs 1375±213.54 vs 771.67±82.19 pg/ml) levels in vitro model following Jmjd3 up-regulation, comparing with Jmjd3 up-regulation (Fig. 6E-6H). PHF20 over-expression increased IL-1β (510±28.06 vs 200±24.75 vs 382.5±18.71 pg/ml), IL-6 (190.67±9.84 vs 67.333± 11.47 vs 117.333±8.99 pg/ml), INF-γ (62.33±3.68 vs 18±2.45 vs 48±2.45 pg/ml) and TNF-α (586.67±32.99

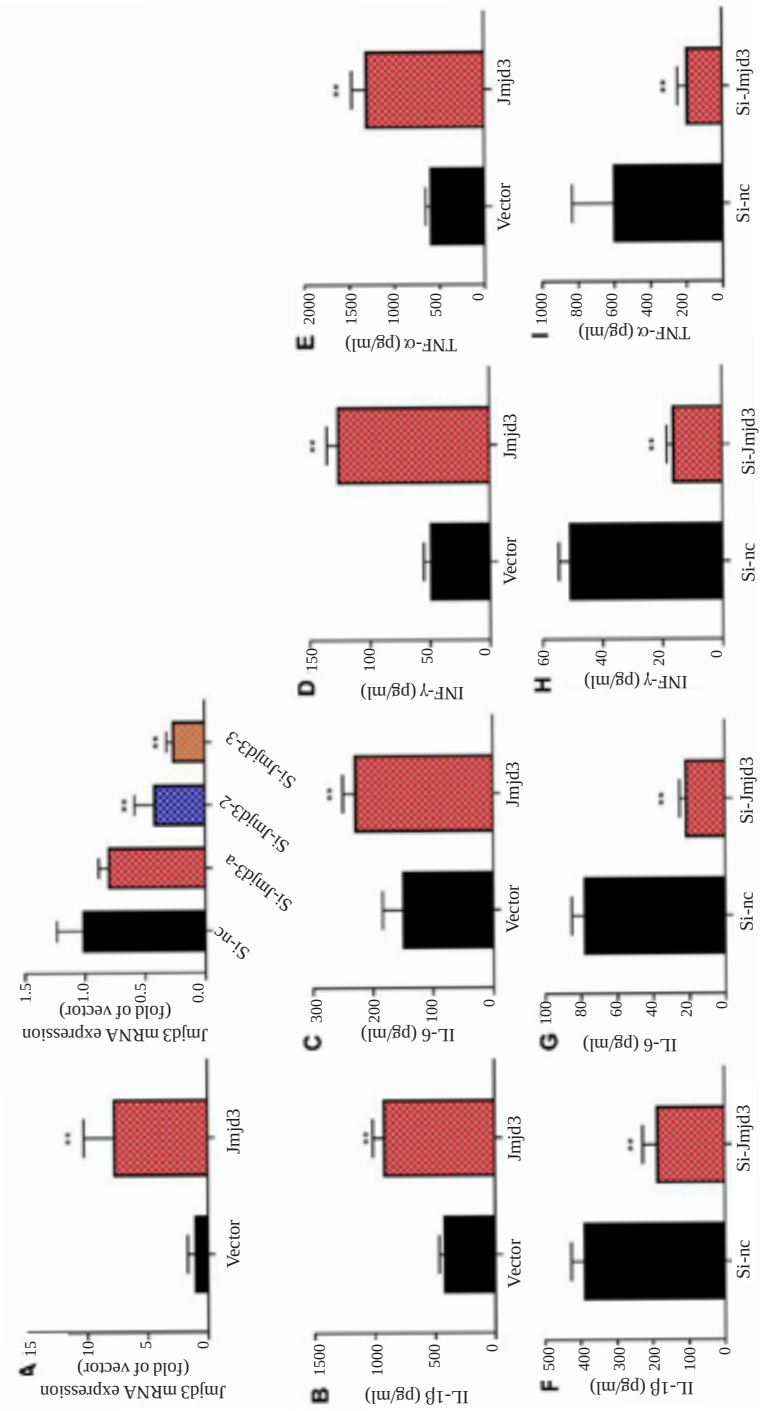

Fig. 2. Jmjd3 promoted inflammation in vitro model of septicemia
Jmjd3 mRNA expression (A);
IL-1β (B), IL-6 (C), INF-γ (D) and TNF-α (E) levels in vitro model by over-expression of Jmjd3 group;
IL-1β (F), IL-6 (G), INF-γ (H) and TNF-α (I) levels in vitro model by down-regulation of Jmjd3 group.
Vector, control negative group; Jmjd3, over-expression of Jmjd3 group;
Si-nc, si-negative group; Si-Jmjd3, down-regulation of Jmjd3 group;
##p<0.01 compared with control negative group or si-negative group

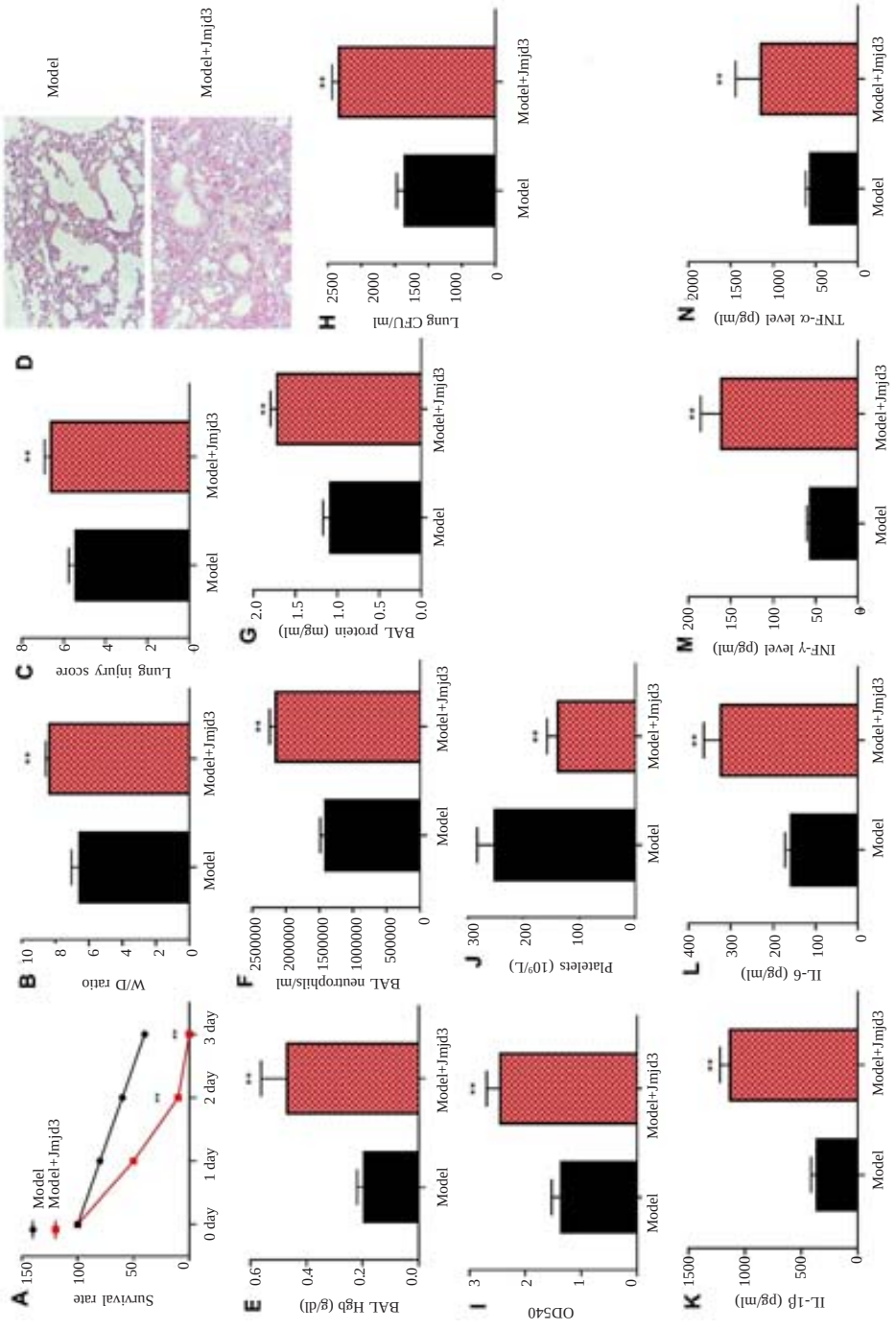

Fig. 3. Jmjd3 promoted septocemia and inflammation in mice model
Survival rate (A),W/D rate (B), lung injury score (C), lung injury (D), BAL fluid hemoglobin (Hgb) concentration (E), BAL neutrophils (F), BAL protein (G), lung bacterial CFU (H), BAL fluid OD540 (I), plateles in BAL (J)
Model, mice model of septocemia; Model+Jmjd3, mice model of septocemia with Jmjd3
****p<0.01 compared with mice model of septocemia group**

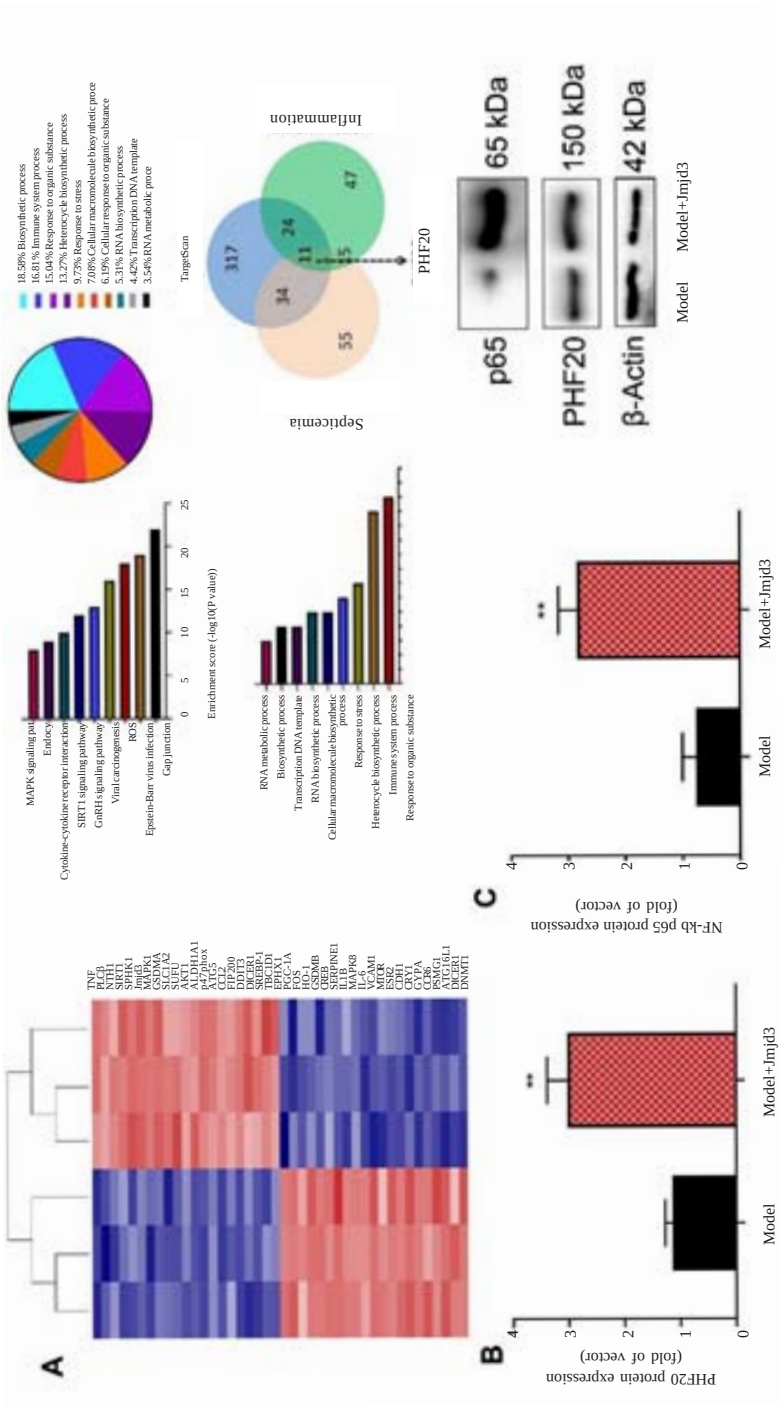

Fig. 4. Jmjd3 induce PHF20/p65 expression in pediatric model with septicemia
Heat map, signaling pathway and analysis results (A), PHF20 and p65 protein expression (B and C)
Model, mice model of pediatric model with septicemia; Model+ Jmjd3, mice model of pediatric model with septicemia by Jmjd3 recombinant protein
****p<0.01 compared with mice model of pediatric model with septicemia**

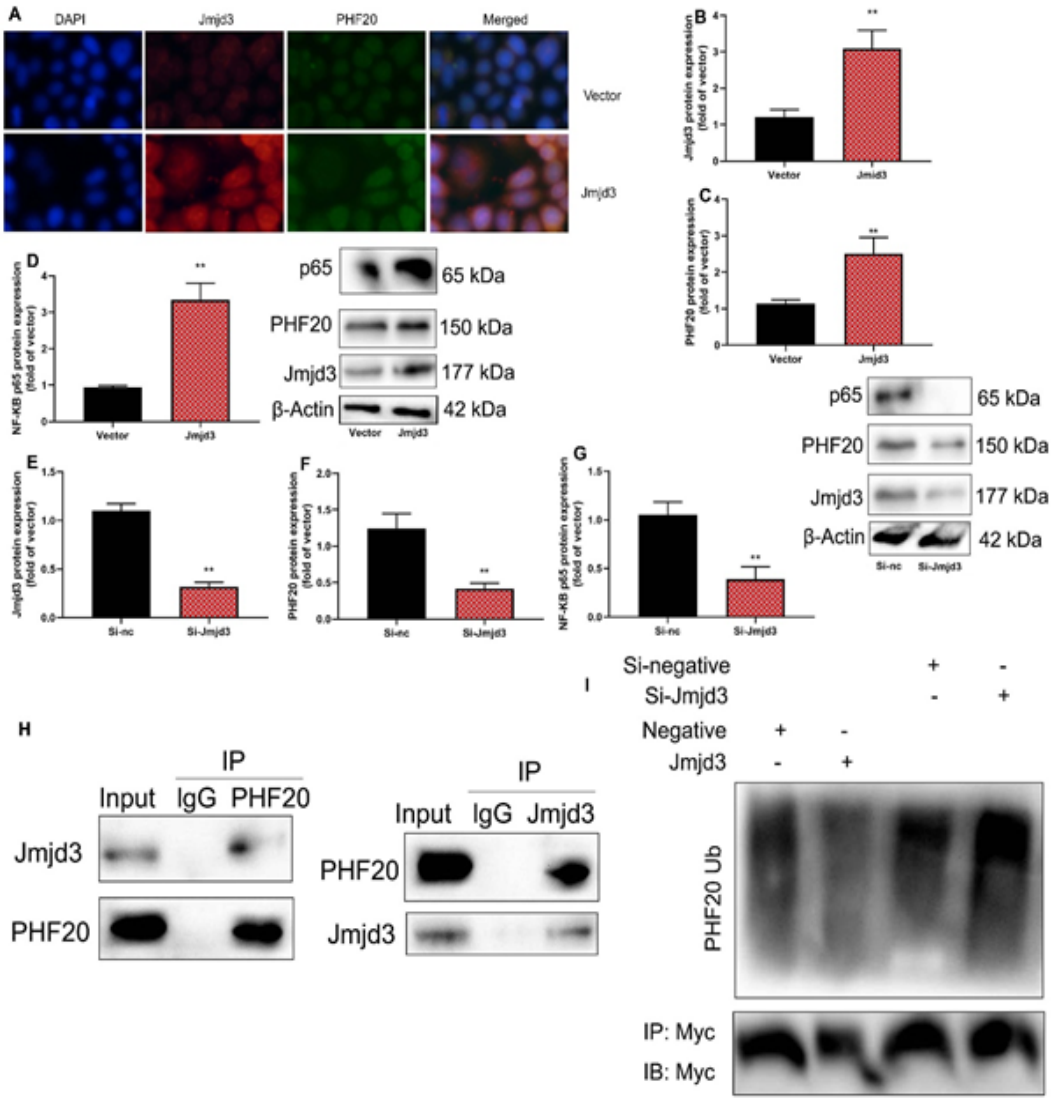

Fig. 5. Jmjd3 induce p65 in pediatric patients with septicemia by PHF20 Ubiquitination
Jmjd3 and PHF20 in vitro model by immunofluorescence (A), Jmjd3 (B), PHF20 (C) and p65 (D) protein expressions in vitro model by over-expression of Jmjd3;
Jmjd3 (E), PHF20 (F) and p65 (G) protein expressions in vitro model by down-regulation of Jmjd3;
The association between Jmjd3 and PHF20 proteins by Co-IP (H);
PHF20 ubiquitination in vitro model (I)
Vector, control negative group; Jmjd3, over-expression of Jmjd3 group;
Si-nc, si-negative group; Si-Jmjd3, down-regulation of Jmjd3 group;
$^{\#\#}$p<0.01 compared with control negative group or si-negative group

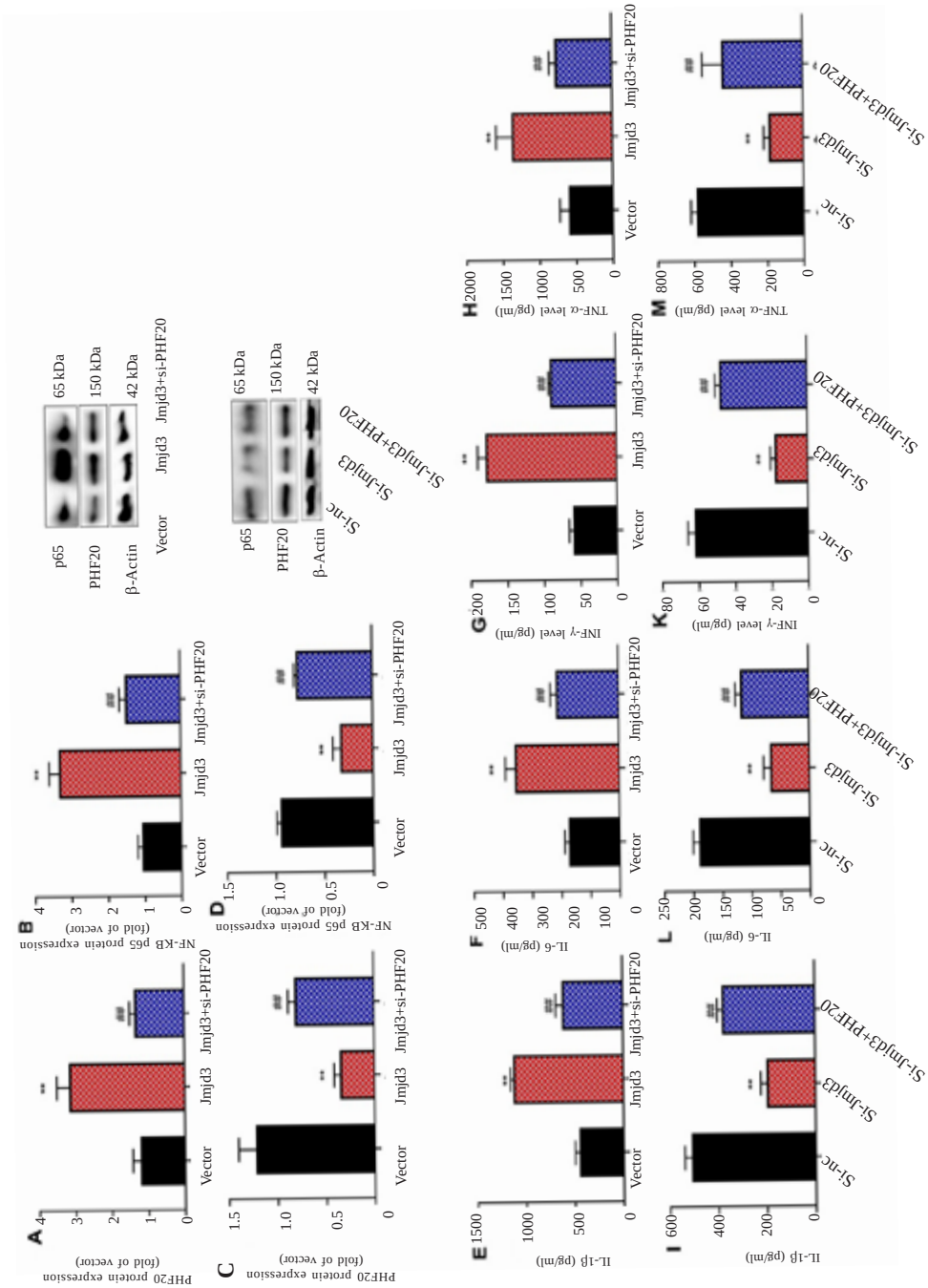

Fig. 6. The regulation of PHF20 control the effects of Jmjd3 in model of septicemia
PHF20 and p65 protein expression (A and B) in vitro model of over-expression of Jmjd3 and p65;
PHF20 and p65 protein expression (C and D) in vitro model of down-regulation of Jmjd3 and p65;
IL-1β (E), IL-6 (F), INF-γ (G) and TNF-α (H) levels in vitro model of over-expression of Jmjd3 and p65;
IL-1β (I), IL-6 (J), INF-γ (K) and TNF-α (L) levels in vitro model of down-regulation of Jmjd3 and p65.
Vector, control negative group; Jmjd3, over-expression of Jmjd3 group; Jmjd3+PHF20, over-expression of Jmjd3 and PHF20 group;
Si-nc, si-negative group; Si-Jmjd3, down-regulation of Jmjd3 group; Si-Jmjd3+si-PHF20, down-regulation of Jmjd3 and down-regulation of PHF20 group
##p<0.01 compared with control negative group or si-negative group

vs 188.33±28.67 vs 445±106.14 pg/ml) levels in vitro model following Jmjd3 down-regulation, comparing with Jmjd3 down-regulation (Fig. 6E-6H).

DISCUSSION

The incidence rate of neonatal septicemia is 1 percent ~20 percent, which can cause systemic infection in children, and is one of the main causes of death of newborns and premature infants Neonatal septicemia refers to the systemic infection caused by bacteria or other pathogenic microorganisms invading the blood circulation in the neonatal period and growing and reproducing in it, producing toxins. Septicemia is a serious systemic infectious disease caused by bacteria invading the host blood and multiplying and releasing many toxic products (Li et al. 2021a). It has no specific clinical manifestations, complex condition and rapid progress (Moon et al. 2021). If timely and effective treatment is not provided, the mortality rate can reach as high as eighty percent, especially the smaller the birth weight, the smaller the age and the poorer immune function of septicemia (Osca-Verdegal et al. 2021). However, the clinical symptoms and signs of septicemia in children are hidden and lack specificity, which brings difficulties to clinical diagnosis. The current laboratory methods cannot meet the needs of rapid clinical diagnosis (Riauwaty et al. 2021). Chen et al. (2018) suggest Jmjd3 promotes IL-1α release in early sepsis.

The PHF protein family is mainly zinc finger protein containing PhD domain (Agrawal et al. 2018). Phf20 is a potential transcription factor, which can specifically recognise methylated lysine. Existing studies have shown that PHF20 is associated with inflammation (Ge et al. 2019). phf20 can bind to p65, and inhibit tumour development by inducing the expression of p65 (Liu et al. 2017). PHF20 pregulates the p53 and p65 subunit of NF-κB complex expressions and transcriptional activities (Gharib et al. 2018). Zhao et al. (2013) demonstrated that Jmjd3 inhibits reprogramming by targeting PHF20 for ubiquitination.

The researchers confirmed the association between Jmjd3 and PHF20 proteins by Co-IP. Jmjd3 reduced PHF20 ubiquitination and si-Jmjd3 increased PHF20 ubiquitination in vitro model.

Similarly, the researchers found that Jmjd3 induces p65 in paediatric mice with septicemia by PHF20 Ubiquitination. Most importantly, Jmjd3 is an upstream factor that controls many key proinflammatory factors via the induction of p65 by the regulation of PHF20 ubiquitination.

CONCLUSION

Taken together, the findings demonstrate a potential factor of Jmjd3 expression levels as an indicator of paediatric sepsis severity. Jmjd3 promoted inflammation by PHF20 Ubiquitination to induce p65 in paediatric patients with septicemia. The researchers identified that Jmjd3 as an pro-inflammatory, affects paediatric sepsis development and it could hopefully become a therapeutic strategy for paediatric sepsis.

RECOMMENDATIONS

In order to treat septicemia, the inhibition of inflammation should be actively recommended to prevent and treat septicemia, especially inflammatory diseases.

ABBREVIATIONS

Jmjd3: Jumonji domain-containing 3
PHF20: plant homeodomain finger protein 20
TNF-α: tumour necrosis factor (TNF)-alpha
NF-κB: NF-kappaB
IL-6: interleukin-6
IL-1β: interleukin-1β
INF-γ: INF-gamma
Hgb: fluid haemoglobin
BAL: bronchoalveolar lavage

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The written informed consents were obtained from all the subjects and this study was approved by the Ethics Committee of the affiliated hospital of Putian University.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

There are no potential conflicts of interest to disclose.

FUNDING

None.

AUTHORS' CONTRIBUTIONS

Maoxin Huang and Zhenzhen Li are responsible for the guarantee of integrity of the entire study, study concepts, literature research, data and statistical analysis, experimental studies, clinical studies, data acquisition, manuscript preparation, editing and review. The author read and approved the final manuscript.

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