



Epidemiology and outcomes of pneumococcal sepsis in children with nephrotic syndrome in a developing country

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Abstract

Background Pneumococcal infections are common in children with nephrotic syndrome. Knowledge of the commonly available serotypes and antibiotic susceptibility will help in prevention and appropriate management of pneumococcal sepsis, especially in resource-limited countries.

Methods Demographic, clinical, and laboratory data on children with nephrotic syndrome and pneumococcal infections were extracted from the electronic medical records.

Results Sixty-three isolates of pneumococci obtained from 60 children with nephrotic syndrome, over a period of 14 years, were included in the study. This represented 18% of all pneumococcal infections occurring in children during the same period. Commonly available vaccines covered up to 58% of all the serotypes causing infection. Severe disease, with shock, intensive care admission and/or meningitis, was observed in 38% children and mortality was observed in 10%. Resistance to commonly used antibiotics was not observed, except for erythromycin.

Conclusions Pneumococcal sepsis was observed to be common in children with nephrotic syndrome and results in significant morbidity and mortality. Commonly used antibiotics were observed to be effective in management of the infections.

Keywords Invasive pneumococcal disease · Nephrotic syndrome · Septicemia · *Streptococcus pneumoniae* · Pneumococcal vaccine

Introduction

Children with nephrotic syndrome (NS) are at an increased risk of invasive infections with encapsulated organisms, especially *Streptococcus pneumoniae*. Invasive pneumococcal disease (IPD) is defined as *S. pneumoniae* isolation from a normally sterile site in a symptomatic person or identification by positive antigen detection, immunochromatography, or polymerase chain reaction from cerebrospinal or pleural fluid [1]. NS is an ideal nesting ground for pneumococcal infections (PnI), the reasons for which are multifactorial.

Nasopharyngeal colonization of *S. pneumoniae* is common, and invasive infections can easily occur during an immunosuppressed state. Dysfunction of the complement system is one of the best-understood causes; normally, encapsulated organisms are effectively tackled by the opsonization provided by the complement system. However children with NS have low levels of complement factors B and I which increase their susceptibility to PnI [2, 3]. Alteration in humoral immunity, due to hypogammaglobulinemia caused by nonselective proteinuria, is another major determinant in the susceptibility to PnI [4]. Depression in cell-mediated immunity, predominantly due to increased suppressor T-cell activity, also contributes to the increased prevalence of PnI. Defective splenic function, presence of oedema and use of immunosuppressive therapy contribute further to the immunosuppressive state and susceptibility to PnI [5].

Data from Israel, over 20 years, observed a prevalence of 15% for serious bacterial infections in children with NS, and *S. pneumoniae* was the predominant organism isolated (23%) [6]. A recent report from northern India reported

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a 44% incidence of major infections in children with NS, with peritonitis being the commonest at 24% and *S. pneumoniae* being the predominant (35%) bacteria isolated from body fluids [7]. Another study from Bangladesh identified *S. pneumoniae* in 94% of positive blood and/or ascitic fluid cultures from children with NS [8]. Undoubtedly, PnI is a significant source of morbidity in children with NS and close attention is warranted concerning the epidemiology and preventive strategies. This retrospective cohort study was undertaken to report the epidemiological and microbiological aspects of pneumococcal sepsis in children with NS.

Methods

Study setting and patient selection

This retrospective study was conducted at the Pediatric Nephrology Department at Christian Medical College, Vellore (3000-bedded tertiary care hospital in South India), with an annual pediatric nephrology outpatient service of nearly 10,000 patients and 300 inpatient admissions. Data on children admitted to the inpatient wards from January 2007 to September 2021 with a diagnosis of NS were retrieved from the electronic healthcare records, as active hospital-based surveillance for *S. pneumoniae* was initiated in 2007. Blood culture was obtained from all patients who had clinical suspicion of infection (fever, features suggestive of meningitis, pneumonia, or spontaneous bacterial peritonitis) along with appropriate haematological and biochemical parameters. Ascitic fluid collection was not obtained in most patients as blood culture yields were deemed adequate as per prior institutional policy. Data from patients with invasive pneumococcal disease and NS were included, and patients with NS secondary to IgA nephropathy/vasculitis, systemic lupus erythematosus, membranous glomerulonephritis, and membranoproliferative glomerulonephritis were excluded. Institutional review board approval was obtained prior to the initiation of the study, *vide* IRB no.14820.

Frequently relapsing NS was managed with long-term alternate day steroids or levamisole as the first line of therapy and failure of these agents would prompt initiation of oral cyclophosphamide or mycophenolate mofetil. Rituximab or calcineurin inhibitors (CNIs; ciclosporin or tacrolimus) were used in case of failure of multiple agents. Children with steroid resistance underwent kidney biopsy, and CNI therapy was initiated. Oedema was managed with furosemide infusion, along with spironolactone and metolazone; diuretic-refractory oedema was managed with albumin infusions. Intravenous immunoglobulin therapy or antibiotic prophylaxis to prevent infections was not practiced.

Definitions used

Nephrotic syndrome and associated terminologies were defined as per Indian Society of Pediatric Nephrology guidelines [9]. Pneumonia was diagnosed if lobar or parenchymal opacities were observed on a chest X-ray. Meningitis was diagnosed in the presence of seizures (not attributable to hypoglycemia, hyponatremia, hypocalcemia, or cerebral sinovenous thrombosis), neck stiffness, cerebrospinal fluid (CSF) analysis, CT, or MRI findings suggestive of meningitis. Severe disease was defined as an invasive pneumococcal disease with shock requiring fluid resuscitation and/or inotropic support, meningitis, intensive care admission, and/or mortality during the first or second episode of pneumococcal infection. Vaccine-covered serotypes were as follows: PCV10 covered 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23 F; PCV13 covered PCV10 serotypes plus 3, 6A and 19A; and PCV15 covered PCV13 serotypes plus 22F and 33F.

Data collection

Data on gender, age at onset, past course of NS, biochemical and haematological parameters, treatment received, and course of disease in the immediate and long-term follow-up (up to 10 years) were collected in a pre-defined collection form. Microbiological data, including serotype of isolates, antibiogram and vaccine susceptibility was collected from the electronic health records. In the case of repeat infections, data on the admission with higher clinical severity was evaluated.

Pneumococcal isolation

The specimens (blood, CSF, and other sterile fluids) were processed as per standard microbiological procedures. The identification of *S. pneumoniae* was done using Centers for Disease Control (CDC, Atlanta, USA) protocols [10]. Serotyping of *S. pneumoniae* isolates was done by Quellung reaction using type-specific pneumococcal antisera from Statens Serum Institut (Copenhagen, Denmark) and sequential customized multiplex polymerase chain reaction (PCR) [11]. The minimum inhibitory concentrations (MIC) were determined using Vitek 2 systems (Biomerieux, USA) and interpreted as per the Clinical and Laboratory Standards Institute (CLSI, USA) guidelines [12].

Statistical analysis

Microsoft Excel (Redmond, Washington, USA) was used to create the database, and Stata (College Station, Texas, USA) v14.0 was used to perform statistical analysis. Categorical

variables were described as frequency (percentage), and continuous variables were described as median (interquartile range [IQR]) or mean (standard distribution) as per the normality of distribution. Univariate logistic regression was used to obtain the odds of severe disease. Factors used in logistic regression were age (children <5 years particularly), low serum albumin (found to be a predictive factor in a previous study), gender, the commonest serotype observed, presence of more than two immunosuppressive agents (presumed higher risk) and initial episode (*versus* relapses; in view of significant proportion of children with onset of NS and PnI) [7, 13, 14].

Results

From January 2007 to August 2021, 2303 admissions were observed in children <18 years of age (for 1,539 unique patients) with a diagnosis of NS, predominantly for edema control, with or without suspected bacterial infection. Among 1077 blood cultures sent (in 790 unique patients), bacterial growth was observed in 196 (18.2%) cultures. Common bacteria isolated included *S. pneumoniae* ($n=65$, 33.2%), coagulase-negative *Staphylococcus* ($n=33$, 16.8%), *Escherichia coli* ($n=23$, 11.7%), *Micrococcus* ($n=14$, 7.1%), *Enterococcus* ($n=9$, 4.6%), and *Klebsiella* ($n=5$, 2.6%). During the same period, a total of 364 pneumococcal infections (septicemia, pneumonia, meningitis or peritonitis) were documented in children (<18 years of age) were managed at the hospital and a significant proportion of those (17.8%) occurred in children with NS. Some of these infections (prior to 2018) were reported previously in reports from our center [15–17]. Institutional culture positivity rates, overall pneumococcal isolate numbers and proportions in children, and children with NS are described in Supplementary Table 1.

Sixty-three isolates of *S. pneumoniae*, obtained from 60 children (70% male; 3 children with repeat infections) with idiopathic NS, all during initial episode or relapse, were included in the study (2 were excluded; 1 each with SLE and IgA nephropathy). PnI occurred at a median of 13 (IQR 3, 37) months after the onset of NS; 18 patients (30%) had PnI at the onset of NS. At PnI, frequently relapsing NS was seen in 8 (13.3%), steroid dependent disease in 16 (26.7%) and late resistance in 3 (5%) of patients; while others (55%) demonstrated infrequent relapses. The median age at presentation with infection was 49 (IQR 33, 88) months (Fig. 1 represents the age groups of children affected). The median serum albumin was 1.2 (IQR 1.0, 1.5) g/dL at presentation with spot urine protein creatinine ratio of 14 (IQR 8, 20). Severe disease was observed in 23 (38.3%) patients with pneumonia in 21 (35%), meningitis in 5 (8.3%), and peritonitis in 2 (3.3%) patients. Mortality

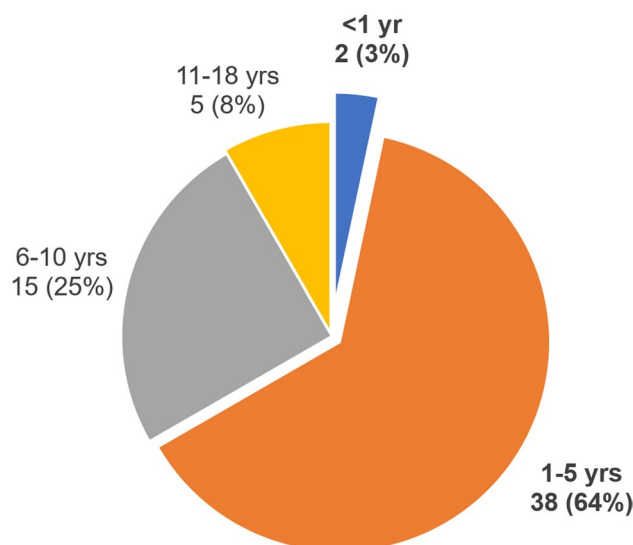


Fig. 1 Age distribution of children with nephrotic syndrome and pneumococcal infection

was observed/presumed in a total of 6 (10%) patients; 3 patients died in hospital (one during the second episode of infection); and 3 others were discharged against medical advice in a critically ill state and were presumed to have succumbed to the illness. All other children recovered without sequelae. Median length of hospital stay was 8 (IQR 5, 10) days, and overall antibiotic duration was 14 (IQR 10, 15) days. Resistance to corticosteroid therapy was observed in 11 (18.3%) patients (5 with initial resistance), during the index episode with PnI. At last follow-up ($n=41$, median 32 months), 29 (48.3%) children were in sustained remission or had infrequent relapses.

Serotype data was available for 60 isolates (57 children; Table 1); serotype 6B and 15B were the commonest serotypes (8 and 7 each). None of the patients had received any pneumococcal vaccine in the past. Nearly 58% of the serotypes associated with PnI would have been covered by available vaccines (PCV10, PCV13 or PCV15; Fig. 2 demonstrates vaccine susceptibility patterns). Antibiotic susceptibility patterns (Table 2) demonstrated high (>93%) sensitivity to all the commonly used antibiotics, including crystalline penicillin, cefotaxime, levofloxacin, linezolid, and vancomycin. Significant resistance (49%) to erythromycin was observed. No multi-drug resistant strains were identified. Factors associated with severe disease (shock requiring fluid resuscitation, intensive care unit admission, or mortality in first or second infection; Supplementary Table 2) were analysed; none were observed to be statistically significant.

Table 1. Pneumococcal serotype frequency observed in the study (N=60)

Parameter	n (%)
6B	8 (13.3)
15B	7 (11.7)
19F	6 (10.0)
6A, 14, 19A, 23F	4 (6.7)
9V, 15C	3 (5.0)
33C	2 (3.3)
4, 6C, 10F, 11A, 13, 21, 24A, 24B, 24F, 25A, 25F/A/38*, 29, 33F, 35B, 47F	1 (1.7)

*25F/A/38 was an organism untypable by Quellung reaction and PCR serotyping provided 25F/A/38; likely due to cross-reaction. Serotype data for 3 isolates were unavailable

Discussion

In this study, we observed *S. pneumoniae* as the predominant organism isolated in blood cultures in children with NS. Other common organisms observed coagulase

negative *Staphylococcus*, *E. coli*, and *Micrococcus*; though coagulase negative *Staphylococcus* and *Micrococcus* are usually regarded as contaminants, isolation may be relevant in the immunosuppressed state of NS. Children with NS shared a significant burden (18%) of all the infections with *S. pneumoniae* in children during the same period. A significant number of infections were diagnosed during the first episode of NS and were associated with radiographic features of pneumonia. Severe disease and significant mortality (10%) were also observed after infections.

The vaccine-preventable serotypes most responsible for IPD in our study (6B, 19F, 6A, 23F) are commonly implicated in both pneumococcal nasopharyngeal carriage and IPD in studies from India and the subcontinent, while serotype 15B, the other common serotype from our study, is one of the commonest non-vaccine serotypes responsible for IPD [18–20]. Serotype 15B has been observed predominantly in nasopharyngeal carriage in other studies [21]. Serotype 1 was observed to cause peritonitis in previous reports; however, no isolates were observed in this study [15]. Serotype 14, a major contributor to pneumococcal meningitis, was

Fig. 2 Vaccine susceptibility patterns of the isolates observed in the study. Serotypes and their respective frequencies are reported on the outer doughnut. PCV10 covered 26 (43%) serotypes, PCV13 covered 34 (57%) and PCV15 covered 35 (58%) serotypes. The green segment demonstrates the additional isolate covered by PCV15. No vaccine coverage was observed in 25 (42%) serotypes

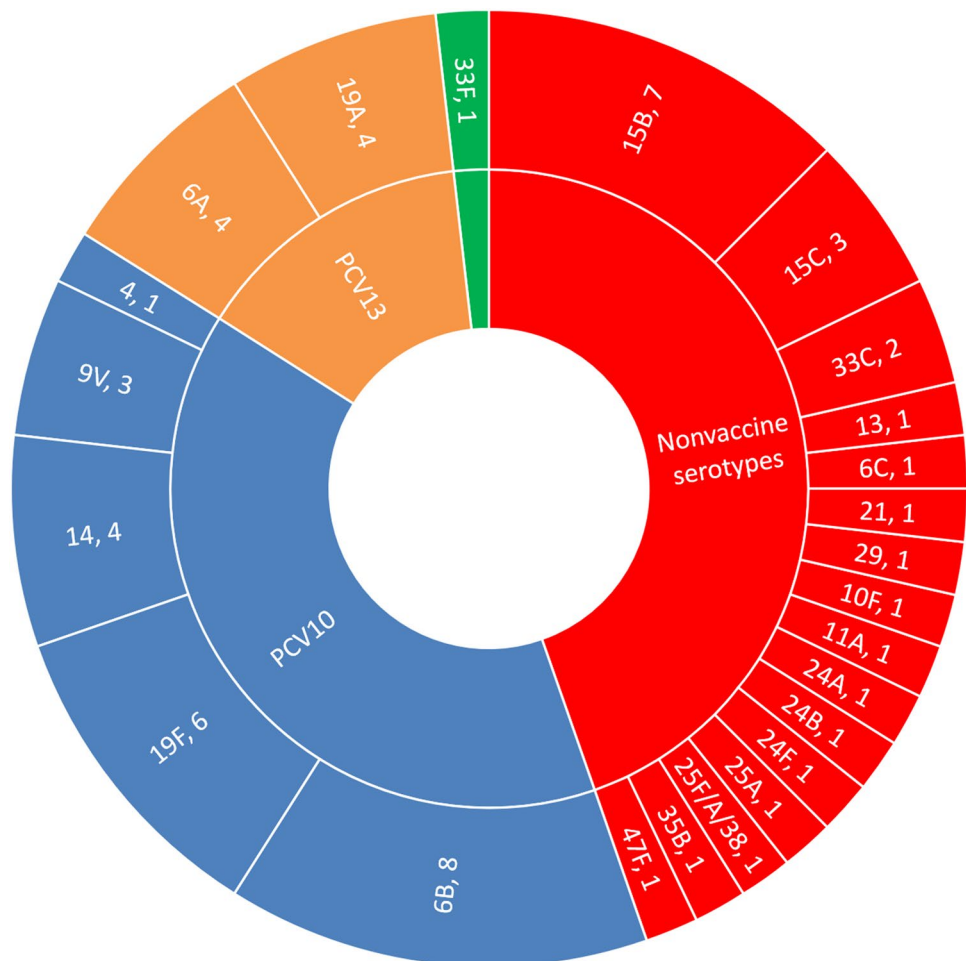


Table 2. Antibiotic sensitivity patterns

Antibiotic	Sensitive	Intermediate	Resistant
Penicillin (<i>n</i> =59)	56 (94.9)	1 (1.7)	2 (3.4)
Meningeal (<i>n</i> =5)	3 (60)	1 (1.9)	2 (40)
Non-meningeal (<i>n</i> =54)	51 (98.1)		
Erythromycin (<i>n</i> =53)	27 (50.9)		26 (49.1)
Chloramphenicol (<i>n</i> =21)	20 (95.2)		1 (4.8)
Cefotaxime (<i>n</i> =55)	55 (100)		
Levofloxacin (<i>n</i> =59)	58 (98.3)	1 (1.7)	
Linezolid (<i>n</i> =59)	59 (100)		
Vancomycin (<i>n</i> =59)	59 (100)		

Sulfamethoxazole-trimethoprim and teicoplanin sensitivity were observed in one tested isolate each. Sensitivity data was unavailable for some isolates for respective antibiotics

less commonly implicated in our children with NS [22]. These differences may in part be due to age-related serotype susceptibility, as the major burden of pneumococcal meningitis is in children under 2 years of age [1], while our children with NS and those with IPD due to the commonest serotypes 6B and 15B were all older at a mean age of 4 years. Most of the serotypes were sensitive to the commonly used antibiotics. It was observed that 43–58% of all pneumococcal infections were by serotypes covered by commonly available vaccines.

Data on the incidence of pneumococcal septicemia in children with NS is scarce; recent data from a developing country reported 73% (33/45) of all culture-positive infections in children with NS being pneumococcal in etiology [8]. A prospective study from northern India observed an incidence of 35% (9/26) for pneumococcal infections in children with NS [7]. Though overall culture positivity rates were low, the burden of pneumococcal infection in children in our study was significant. The Department of Clinical Microbiology at CMC Vellore has been functioning as a South East Asia Regional Reference Laboratory for pneumococcal surveillance for the last 22 years [20, 23]. The significant number of culture positivity rates and pneumococcal isolates truly reflect the epidemiology of PnI in our cohort, due to the robust and meticulous techniques employed in the laboratory work.

In general, the antibiogram represents a favorable response to commonly used antibiotics, despite the rampant and unscrupulous use of antibiotics in the general community. Only a small proportion of children received any antibiotic therapy before admission. This may be due to increased parental anxiety for a child with chronic illness, leading to direct presentation to the tertiary care center, rather than going to the primary care physician. Hence, these children were shielded from over-the-counter antibiotic therapy, widely prevalent in the community. High rates of erythromycin resistance are observed in this report, consistent with

the data obtained from national surveillance [1]. Overall, common antibiotics like penicillin and third-generation cephalosporins seem to be a reasonable choice for empiric therapy in suspected pneumococcal sepsis in children with NS, with third-generation cephalosporins preferred in those with signs of meningitis due to penicillin resistance in over a third of meningeal isolates, similar to data already published from our institution [24].

Infections are known to trigger relapses of NS; however, an interesting observation of nearly a third of patients having PnI at the onset of NS was made in this cohort. The possibility of pneumococcal infections being a trigger for the onset of NS may be more than speculation, akin to novel coronavirus (SARS CoV2) reportedly triggering various glomerular diseases [18, 19, 22, 25, 26]. Respiratory tract infections were observed to be the commonest infections in children at the onset of NS and a few reports mention identification of *S. pneumoniae* as the culprit organism [13, 27, 28]. Infections are also known to be a significant risk factor for acute kidney injury in children with NS; however, it was not commonly observed and was not explored in this study [29].

Antibiotic prophylaxis against pneumococcal (or any other) infection was not practiced routinely at our institution. Though current guidelines and a previous Cochrane systematic review do not recommend the use of prophylactic antibiotics against PnI in children with NS in view of scarce or poor evidence, some authors suggest that antibiotic prophylaxis may be used in children <2 years of age with relapsing disease and prior PnI [30–35]. However, the risk of antibiotic-resistant organisms poses a significant threat in children on prophylaxis [36, 37].

Our study is strengthened by good yields of blood culture in identifying bacterial organisms in children with NS. Detailed serotyping and antibiogram gave a comprehensive microbiological aspect of the *S. pneumoniae* sepsis in our patients. The absence of ascitic fluid examination may be a limitation for our study; however previous reports have observed that bacterial growth from ascitic fluid is low at around 3%, less than one fourth that of blood culture [7, 8].

None of the children with pneumococcal infections had received any dose of any pneumococcal vaccine, reflecting the low prevalence of vaccination during this period. Pneumococcal vaccines were not included in the national immunization schedule till 2017, after which Government of India has initiated free pneumococcal vaccination in the national schedule in a phased manner and the state of Tamil Nadu has implemented this from July 2021 onwards [38]. Two publications provide data from 2012 to 2021 and data from 2007 to 2021 was unavailable. One hospital-based surveillance study from six states, with data from 2012 to 2017, reports a vaccination coverage of 0.3–0.5% in children with PnI [1]. Another report, which looked at real-time monitoring of the pneumococcal vaccine in rural India using a digital tracking platform in a district from Rajasthan from 2017

to 2020, reports 96% of children receiving first dose and 44–76% of children receiving the third dose at <12 months of age [39]. It is to be observed that this study population represents one of the states implementing the vaccination program, and the study population represents a minuscule amount of the country's population. Currently, the best estimated vaccine coverage of 3 doses of pneumococcal vaccination is provided by a WHO/UNICEF document, which puts it to around 15% [40].

The current cost of a single pneumococcal vaccine dose on the open market in India ranges from 1600 to 3200 Indian national rupees (INR) which translates to 20–40 US dollars (USD); and three doses are usually unaffordable to most people in the lower or lower-middle socioeconomic strata. However, an average inpatient stay for 8 days in our hospital usually costs INR 15,000–20,000 (USD 200–300), not to mention the expenses incurred from loss of wages for the caregivers. The introduction of the PCV vaccination program was estimated to cost an additional USD 467 (INR 35,254) for averting one disability-adjusted life year, which is less than the one-time gross domestic product per capita of India [41]. The effect of this welcome step of vaccinations in the government schedule, free of cost, aimed at reducing PnI morbidity and mortality is likely to be reflected in future studies, although an epidemiological shift from vaccine serotypes to non-vaccine serotypes responsible for pneumococcal illness may be expected as vaccination rates increase.

Conclusion

Infection with *S. pneumoniae* accounted for a significant proportion of sepsis in children with NS; resulting in severe disease in a large number of patients and high mortality. Commonly used antibiotics continue to be effective in management. It was observed that more than half the infections could have been prevented by commonly available vaccines. It is imperative to increase vaccine coverage to reduce the prevalence of pneumococcal infections.

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s00467-022-05550-0>.

Data availability The datasets generated during and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions GM conceptualized and designed the study. GM, ASG, and RV made substantial contributions to the acquisition, analysis, and interpretation of data. GM and ASG drafted the manuscript. DRV, WR, VPV, BV, and IA made substantial contributions revised the work critically for important intellectual content. GM agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy and integrity of the work are appropriately investigated and resolved. All authors approved the final version of the manuscript.

Declarations

Ethics approval Institutional ethics committee approval was obtained before commencement of the study.

Consent to participate As it was a retrospective study, obtained completely from electronic medical records with deidentified patient details, consent was not deemed necessary by the Institutional Review Board.

Conflict of interest The authors declare no competing interests.

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