The impact of COVID-19 pandemic on neonatal admission: an interrupted time-series study

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Abstract: (1) Introduction: The unprecedented coronavirus disease 2019 (COVID-19) epidemic has caused millions of infections worldwide and represents a significant challenge facing modern health care systems. This study was conducted to investigate the impact of lockdown measures on regional neonate services, which might be used to predict the long-term effects of medical behavior. (2) Methods: Using hospital information system (HIS) Statistics data from 4 January 2019 to 27 August 2020, an interrupted time-series analysis was employed to compare changes and trends in hospital admissions and disease spectrum before and after the lockdown interventions. Furthermore, this study was designed to evaluate whether the pandemic influenced newborns' healthcare behavior. (3) Results: Overall, 13,540 infants were admitted to the NICU during the pre-COVID period (n = 12082) and COVID-impacted period (n =4558). The patients' age at admission were younger than that of the pre-COVID-19 period (median age 5d vs. 6d after birth, $p < 0.001$). The overall number of neonate visits consistently decreased from the first days of the lockdown measures (24 January 2020). The disease spectrum for respiratory system, infectious diseases, and gastrointestinal disease indicated no declined immediately after intervention($p =0.079$, $p =0.113$, $p =0.060$, respectively). There was an immediate decline in the volume of Jaundice-related conditions ($p<0.001$) after lockdown measures. The percentage of patients who suffer from respiratory system and infectious diseases has decreased ($p =0.005$ and $p =0.002$). However, a relatively high percentage of patients admitted to the neonatal intensive care unit (NICU) presented with Jaundice-related conditions ($p <0.001$). (4) Conclusions: In summary, the COVID-19 pandemic profoundly impacted the regional neonate services. However, it is still unclear what might be the effect of long-term effects from pandemic.
Keywords: COVID-19; pandemic; lockdown; Neonate services; disease spectrum; interrupted time-series analysis

1.Introduction

Since December 2019, an outbreak of pneumonia caused by Coronavirus disease 2019 (COVID-19) was first reported in Wuhan, China[1].COVID-19 was declared a pandemic by the World Health Organization, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on 11 March 2020[2]. As of this writing（December 1, 2020）, the pandemic has been confirmed in nearly 63 million individuals worldwide and causes at least 1,400,000 deaths[3]. To control the rapid spread of this viral disease, on 23 January 2020, the Chinese government raised its national public health response to the highest state of emergency in Wuhan, China. The government has enacted a series of lockdown strategies, including city-wide lockdowns, screening measures at train stations and airports, school closure and non-essential businesses were suspended[4]. Non-pharmacologic public health interventions cause a novel challenge for healthcare systems. In recently published studies, Lockdown effects have caused a noticeable reduction in both adult and pediatric patient volumes during the COVID-19 pandemic[5-7]. However, to the best of our knowledge, there are no reports on the changes of newborn patients demographics information. This study was conducted to investigate the impact of lockdown measures on neonatal admissions and disease spectrum, which can also be used to predict the long-term effects of newborn medical

behavior.

2. Methods

2.1. Study setting

The Department of Neonatology of Children's Hospital of Chongqing Medical University, one of the regional neonate emergency care providers and the most extensive local neonate referral center in southwestern China, serves approximately 10,000 babies annually last five years. The Department of Neonatology is a 310-bed academic medical center with advanced medical equipment and is staffed by neonatologists, fellows, pediatric residents, and registered nurses. Besides, it offers a comprehensive range of services to the districts of Chongqing and neighboring provinces, including Guizhou, Sichuan, Yunnan, and Tibet.

2.2. Data resources and intervention

Clinical data and demographics information were collected from the hospital information system (HIS) between 4 January 2019 and 27 August 2020. This Clinical information collected includes the volume of admissions and neonate transport, sex, age (days), admissions, length of hospital stay(days), treatment, and disease spectrum.

Chongqing government initiated the first-level response to major public health emergencies and implementation of lockdown strategies since 24 January 2020[8]. We designated two periods for analysis purposes: a stable pre-COVID period, reflecting routine workload of department of Neonatology（55 weeks from 2019.1.4–2020.1.23）and a COVID-impacted period (31 weeks from 2020.1.24–2020.8.27). The time unit chosen was one week to provide optimal precision to the model.

2.3.Outcomes

The primary objective was to detect changes in levels and trends of hospital admissions and disease spectrum before and after the lockdown interventions and assess the impact of control measures. Furthermore, this experiment was designed to evaluate whether or not the pandemic has influenced newborns' healthcare behavior.

2.4.Statistical analysis

Interrupted time series（ITS）is a suitable model for assessing the short- and long-term effects of interventions in a quasi-experimental study[9]. The segmented regression model is one of the most commonly used methods for ITS methods[10]. The following segmented linear regression model was applied

$$Yt= \beta0 + \beta1* time+ \beta2* intervention +\beta3* postslope + \varepsilon t$$

Time (in weeks) was treated as a continuous variable indicating that volume of weeks from the observation time to time t. Intervention is a dummy variable indicating the pre-lockdown period（coded 0）or the post-lockdown period（coded 1）. Postslope is a continuous variable, pre-intervention code 0; post-intervention takes the same value as the time variable.β1 represents the estimate the baseline level of outcome at time zero before the lockdown; β2 estimate the level change in the rate immediately after the intervention; β3 is changes in trend after the lockdown, and εt is the error term of the model[11,12]. The Durbin–Watson (DW) method was used to detect and exclude the time series data's stability. Values approaching 2 and 4 mean almost no autocorrection, whereas 0 indicates positive autocorrection. The generalized linear model（Prais-Winsten estimates）should be used to estimate the most efficient way to estimate the value.

Descriptive analyses, including the mean and interquartile range as appropriate, were performed to describe the Characteristics of Infants during the Pre‐COVID and Intervention periods. Student's t-test, Wilcoxon Mann–Whitney test, Pearson chi-squared test were used where applicable to compare demographic and outcome characteristics between the Pre‐COVID and Intervention periods. A *p*-value less than 0.05 was considered statistically significant, whereas a *p*-value less than 0.01 was considered highly significant.

All computations were conducted in RStudio 1.0.44 (RStudio, Inc.) with R v.4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

2.5. Ethics statement

Ethics approval was obtained from the Children's Hospital of Chongqing Medical University Human Research Ethics Committee (Approval No.2020206-1).

3. Results

The weekly volume of neonatal admissions was analyzed between 4 January 2019 and 27 August 2020. Overall, 13,540 infants were admitted to the NICU during the pre-COVID period (n = 12082) and COVID-impacted period (n =4558). The overall number of neonate visits consistently decreased from the first days of the lockdown measures (24 January 2020). Then it was reduced to a nadir of 108 people (between 14 February 2020 and 20 February 2020). Afterwards, the results show a slow recovery of progression in the number of hospital admissions. Still, it would take a more time to return to the pre-COVID period levels (Figure1).

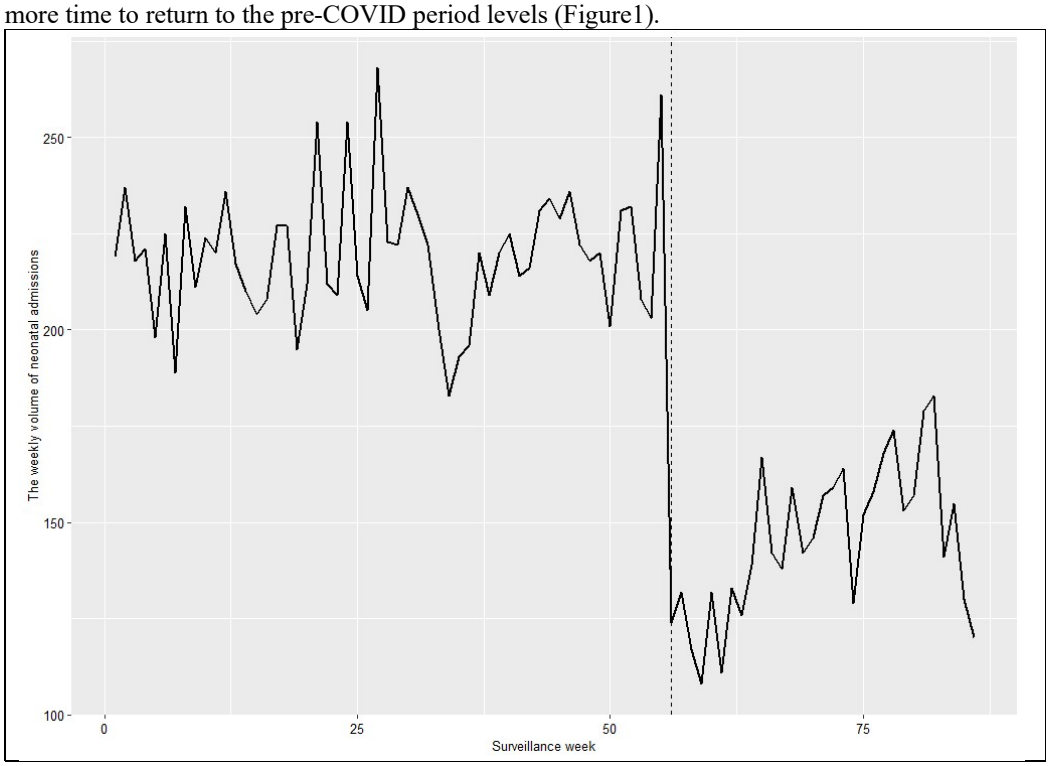


Figure 1. Weekly volume of neonatal admissions visits — Children's Hospital of Chongqing Medical University, China, 4 January 2019–27 August 2020. The vertical black dashed lines indicate the time of implementation of lockdown strategies since 24 January 2020.

Due to the epidemic of COVID-19, the proportion of emergency and inter-hospital transfer increased, while the outpatient ratios decreased. The patients seeking consult were younger than the pre-COVID-19 period (median age 5d *vs*. 6d, $p<0.001$). In the COVID-19 period, 58.8% of all visits were in children aged ≤7days old, compared with 54% during the pre-COVID period. In the pre-COVID period, Patients were hospitalized for a median of 6 days (*IQR*: 4 - 10 days), which increased to 7 days (*IQR*: 5 - 13 days) in the COVID period ($p<0.001$). The comparison of the two periods in terms of patients' demographic parameters was showed in Table 1.

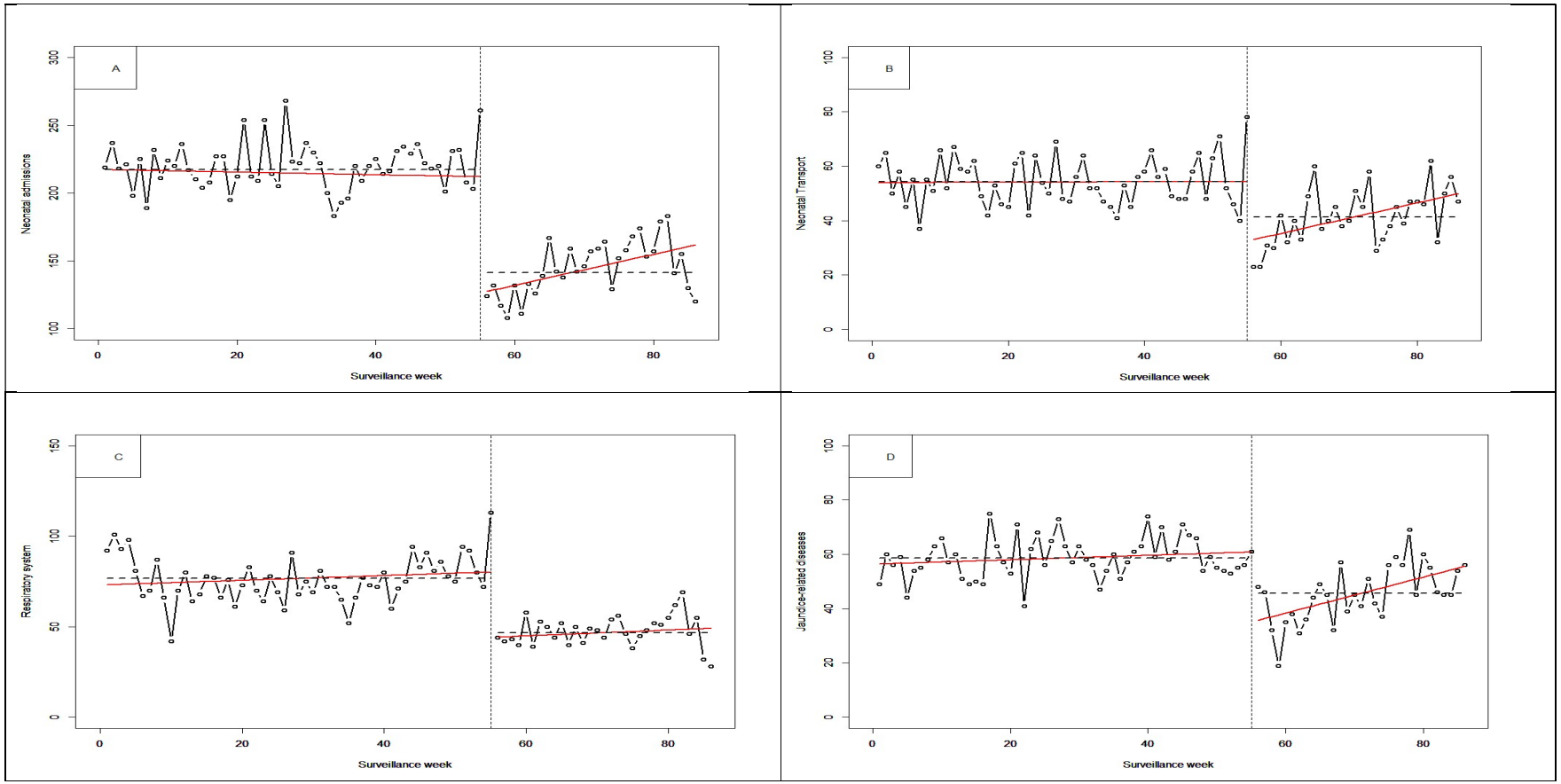
Table 1. Demographic Characteristics for the patients

Variable		Pre - COVID	COVID impacted	*p* value
Total		12082	4558	
Age (days)，median (IQR)		6（1-17）	5（1-14）	<0.001***
Number of patients (%)	≤7 (days)	6613（54.7）	2682（58.8）	<0.001***
	>7 (days)	5469（45.3）	1876（41.2）	
Sex, n (%)	Male	6772(56.1)	2674(58.7)	0.003**
	Female	5310(43.9)	1884(41.3)	
Admissions, n (%)				<0.001***
Emergency		1147（9.5）	611（13.4）	<0.001***
Outpatient		6695（55.4）	2060（45.2）	<0.001***
Transfer from other medical		4240（35.1）	1887（41.4）	<0.001***

facilities, n (%)				
Neonatal Transport from, n (%)	main urban areas	2683（89.7）	1157（89.8）	0.943
	suburban areas	308（10.3）	131（10.2）	
Disease spectrum, n (%)				<0.001***
Respiratory system		4191(34.7)	1474(32.3)	0.005 **
Infectious diseases		686(5.7)	204(4.5)	0.002 **
Gastrointestinal system		1513(12.5)	604(13.3)	0.208
Jaundice-related diseases		3227(26.7)	1413(31.0)	<0.001***
Others		2465(20.4)	863(18.9)	0.035*
Treatment, n (%)	Surgery	498(4.12)	214(4.70)	0.1032
	Exchange transfusion[a]	66(2.05)	31(2.19)	0.7446
	Therapeutic hypothermia	52(0.43)	44(0.97)	<0.05*
	Mechanical ventilator[b]	1094(26.1)	308(20.9)	<0.001***
Length of hospital stay (days), median (IQR)		6（4-10）	7（5-13）	<0.001***
Number of patients (%)	< 7 (days)	7127(59.0)	2326(51.0)	<0.001***
	＞7 (days)	4955(41.0)	2232(49.0)	

Median (interquartile range, IQR) for continuous variables, number (%) for categorical variables
a Percentage of Exchange transfusion in the Jaundice-Related Diseases groups.
b Percentage of Mechanical ventilator in the Respiratory system groups.
Statistical differences: * $p< 0.05$ ** $p < 0.01$, *** $p< 0.001$

After 1-order differencing was used, the differenced sequence tended stationary. All of the Durbin-Watson statistics were approaching 2, indicating that there was no autocorrelation in the observations. When the intervention was implemented on 24 January 2020, the volume of neonatal transports and admissions declined sharply ($p<0.001$). With the improvement of the epidemic situation, the observation shows that the slow-growth trend for the volume of neonatal transports and admissions ($p =0.003$ and $p =0.014$) (Table2 and Figure2).
The volume of newborns suffer from respiratory system, infectious diseases, and gastrointestinal disease indicated no declined immediately after intervention ($p =0.079$, $p =0.113$, $p =0.060$, respectively). However, there was an immediate decline in the volume of patients complaining about Jaundice-related conditions ($p<0.001$) after lockdown measures (Table2 and Figure2).
In the intervention period, the percentage of patients who suffer from respiratory system and infectious diseases has decreased ($p =0.005$ and $p =0.002$). However, a relatively high percentage of patients admitted to the neonatal intensive care unit (NICU) presented with Jaundice-related conditions ($p <0.001$). The Surgical and Exchange transfusion proportion was unaffected by these measures ($p =0.103$ and $p =0.745$). However, the Proportion of Therapeutic hypothermia increased ($p <0.05$), while Mechanical ventilator ratios decreased ($p <0.001$) (Table1)



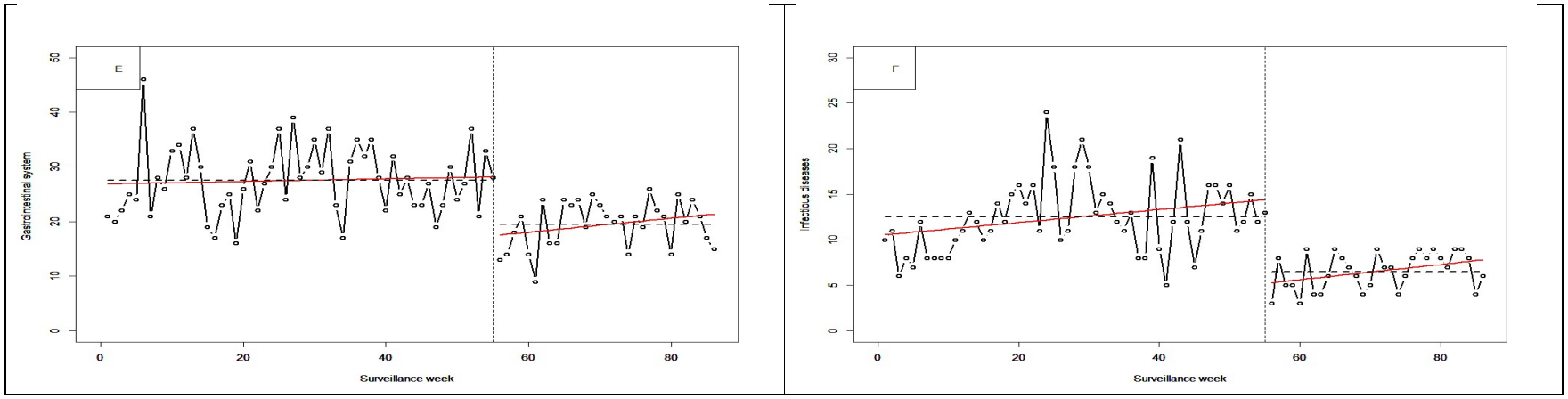


Figure 2. Impact of interventions on attendances and disease spectrum based on segmented regression analysis between 4 January 2019 and 27 August 2020. Vertical black dashed lines represent change-point (Chongqing lockdown on 24 January). The black points in the plot represent weekly changes in the volume of admissions and disease spectrum. The red fitted lines are from Prais-Winsten estimates. Dashed horizontal lines indicate the level change. (A) Neonatal admissions (B) Neonatal Transport (C) Respiratory system (D) Jaundice-related diseases (E) Gastrointestinal system (F) Infectious diseases

Table 2. Estimated Coefficients of the Segmented Regression Model for neonate attendances and disease spectrums since 4 January 2019–27 August 2020.

Variable	Coefficient	Estimate	Std. Error	*t*-value	*P*-value
Neonatal admissions	Intercept β0	217.077	5.249	41.354	<0.001 ***
	Baseline trend β1	0.097	0.16285	0.596	0.553
	Level change after intervention β2	-153.637	27.9172	-5.503	<0.001***
	Trend change after intervention β3	1.046	0.417	2.506	0.014*
Neonatal Transport	Intercept β0	53.837	2.293	23.476	<0.001***
	Baseline trend β1	0.018	0.071	0.254	0.799
	Level change after intervention β2	-52.845	12.295	-4.298	<0.001***
	Trend change after intervention β3	0.553	0.183	3.026	0.003*
Respiratory system	Intercept β0	72.994	4.067	17.944	<0.001***
	Baseline trend β1	0.130	0.125	1.042	0.300
	Level change after intervention β2	-37.848	21.337	-1.774	0.079
	Trend change after intervention β3	0.031	0.321	0.099	0.921
Jaundice-related diseases	Intercept β0	56.345	2.374	23.735	<0.001***
	Baseline trend β1	0.081	0.073	1.105	0.272
	Level change after intervention β2	-57.833	12.633	-4.578	<0.001***
	Trend change after intervention β3	0.582	0.188	3.084	0.003**
Gastrointestinal system	Intercept β0	26.837	1.620	16.561	<0.001***
	Baseline trend β1	0.023	0.050	0.476	0.635
	Level change after intervention β2	-16.461	8.653	-1.903	0.060
	Trend change after intervention β3	0.104	0.129	0.807	0.422
Infectious diseases	Intercept β0	10.484	1.173	8.938	<0.001***
	Baseline trend β1	0.071	0.036	1.963	0.053
	Level change after intervention β2	-9.867	6.158	-1.602	0.113
	Trend change after intervention β3	0.012	0.092	0.133	0.895

Statistical differences: * $p< 0.05$ ** $p < 0.01$, *** $p< 0.001$

4.Discussions

Chongqing, one of the municipalities in China, is among the high-risk region of SARS-CoV-2 spread in China. As of this writing (1 December 2020), Chongqing has reported 590 confirmed cases and 6 COVID-19-associated deaths[8]. As the Chongqing government has implemented a series of lockdown measures after 24 January 2020, these data showed a significant reduction in hospital admissions. This is in keeping with published data from other cohorts in many countries that a range of decline in hospital admission. In the United States, visits and access to the Department of Veterans Affairs hospitals declined by 42% in the COVID-19 period[13]. In France, the number of pediatric emergency department (PED) visits and related hospital admissions after the lockdown decreased by -68% and -45%, respectively[6]. With the improvement of the epidemic situation, neonatal entries' volume is slowly evoking ($p= 0.0142$). Still, it would take a long time to return to the pre-epidemiological levels.

The reason for the observed reduction in neonate visits after the strictest lockdown measures remains unclear. There is a common understanding that hospital admission decreased due to the most stringent lockdown measures and worried about becoming infected by SARS-CoV-2 in

hospital[14,15]. "Mild cases" patients are prepared to go to a local health center rather than to a regional neonate care provider provided that medical resources are available. On the other hand, thanks to the Internet's development, parents can address some or even all of their newborns' problems through effective online counseling, resulting in smaller volume of neonatal outpatient and emergency visits.

As a unique group characterized by immaturity, neonates are susceptible to multi-organ involving disorders (e.g., complicated pneumonia and jaundice, complicated sepsis and necrotizing enterocolitis). The classification of our disease spectrum is based on the primary complaint and the first diagnosis. This report showed that the proportion of admissions for related respiratory system diseases (e.g., neonatal pneumonia, acute respiratory distress syndrome) and infectious diseases (e.g., neonatal sepsis, meningitis) decreased after public health interventions. This may be partially attributed to the reduction in social activities and the emphasis on personal protective equipment (e.g., hand-wash, wearing a mask)[16]. However, the percentage of Gastrointestinal system and Surgery was unaffected by these measures (p=0.208 and p=0.103). This is partly due to the fact that gastrointestinal disorders are relatively more common in newborns due to inborn anomaly (e.g., megacolon, Esophageal atresia, pyloric hypertrophic obstruction)[17]. Some of these diseases require surgical intervention in the neonatal period. As one of the regional neonate emergency care providers and the most extensive local neonate referral center, only the children's hospital was eligible to perform these surgical operations.

Almost all newborn infants develop yellowing of skin and sclera[18,19]. It was hypothesized that lockdown measures might not have a noticeable effect on the volume of jaundice-related diseases admitting to neonatal centers. However, our single-center study showed a significant decrease in jaundiced patients' admissions when public health interventions were implemented. This phenomenon might be partly attributed to the early and stringent preventive measures and partly due to parents' insufficient awareness to pathological hyperbilirubinemia (jaundice may be a "mild" disease, which can also be handled by neighboring hospitals). However, it is observed that the rebounding trend (p= 0.003) was associated with the relaxation of lockdown measures and families seeking better medical resources.

An increase in the average length of stay and precisely the number of patients staying for 7 or more days was seen during the COVID-19 pandemic. The greater length of stay may indicate an increase in the severity of conditions presented to the Newborn Team[20]. Meanwhile, an elevated proportion of therapeutic hypothermia ($p<0.05$) also indirectly reflected that the epidemic had elevated the threshold for inpatient hospitalization to some extent.

4.1. Implications of findings

Since the outbreak of COVID-19 epidemic, there have been dramatically changes on admissions of neonate and healthcare behavior. The volume of hospital admissions has dropped obviously, especially that of mild cases. Medical resources have been more efficiently allocated to critically ill neonates. During this epidemic, the use of video-conferencing and telephone counseling for neonatal follow-up has increased significantly - and it will likely need to continue to do so in the future - and may improve patient experience with fewer journeys to hospital and increased availability of outpatient appointments. Other measures, such as encouraging people to wear a face mask and to follow the principles of personal hygiene, especially hand-washing and suitable social distance, might reduce the morbidity and mortality of respiratory tract diseases and infectious disease to some degrees. Finally and the most important, a possible second wave of the epidemic could take place after lifting the restrictions. Therefore, establishing an effective hierarchical diagnosis system's guidance to guide medical resources distribution is of great importance. Meanwhile, timely transferal for critically ill newborns might be an effective response to improve their prognosis.

4.2. Strengths and limitations

To date, this is the first evaluation of the impact of COVID-19 pandemic on neonatal admission in southwestern China. This relatively large sample size from the database greatly enhances the representativeness of the findings to Chinese population and the countries with limited medical resources. Many previous studies based on lockdown measures reported demographic changes instead of clinical outcomes, whereas those reported outcomes did not demonstrate long-term effects of pandemic on medical behavior[21-23]. This report is one of few those demonstrating changes in relation to medical behavior as well as sustainability for at least 31 weeks after its intervention.

To strengthen methodology, an interrupted time series model was employed for analysis. Interrupted time series regression analyses is regarded as the strongest "quasi-experimental" approach and particularly useful when a RCT is infeasible [9,24], as the case for when lockdown measures were implemented in China. This analysis also provides comprehensive estimates of trends changes linked to the implementation of lockdown measures and early-lift of lockdown measures with various extents. Indeed, the recent upward trends in the volume of admissions are consistent with our simulated scenarios.

There are several potential limitations of this study that should be addressed. First, the main limitation is that a single-center design involving a small sample size. Therefore, it does not have strong universal validity. In addition to the non-pharmacologic public health interventions, neonate services might have been affected by confounding factors, such as different health care resources and health care systems, diverse demographic composition, and variable fertility rates. This study needs further exploration to overcome the above limitations with other databases.

5.Conclusions

In summary, COVID-19 pandemic profoundly impacted the region's neonate services. However, it is still unclear what might be the effect of long-term effects from pandemic. The impacts of COVID-19 in neonate would go far beyond health, including psychosocial, economical, and others beyond this article's scope.

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Conflicts of Interest: The authors declare no conflict of interest

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