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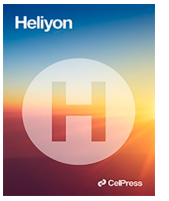

Associations between laboratory variables and clinical features in patients hospitalized with COVID-19 after non-mRNA vaccination in China: A cross-sectional study

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ABSTRACT

Objectives: Based on the data during the outbreak of COVID-19 in Wuxi city in China, we explored the relationship between laboratory variables and clinical features in patients hospitalized with COVID-19 after non-mRNA vaccination, and attempted to identify the significant impact of vaccination and COVID-19 infection on humans.

Methods: A retrospective observational cohort study was carried out. Patients who received non-mRNA COVID-19 vaccines and were hospitalized with COVID-19 between June 28, 2022, and July 24, 2022 were included. The correlation between different vaccine statuses, the time to negative PCR test, and biochemical parameters were investigated.

Results: All patients had a mild COVID-19 disease. The number of vaccine doses exerted no effects on the time to negative PCR test ($P = 0.559$). No differences were evident among inactivated, adenoviral-vectored, and recombinant subunit vaccines in the time to negative PCR test.

Patients who just received one dose had significantly lower blood glucose levels than those who received three doses ($P = 0.024$), whereas two doses had no effect on blood glucose levels (one dose vs. two doses, $P = 0.223$; two doses vs. three doses, $P = 0.457$).

Body temperature ($\beta = 0.168$, $P = 0.011$) and the percentage of lymphocytes ($\beta = -0.219$, $P = 0.001$) were substantially correlated with the time to COVID-19 negative PCR test. The prolonged stay was linked to a rise in GOT that fell within the usual range ($P = 0.025$).

The percentage of lymphocytes ($P = 0.007$) and serum potassium ($P = 0.004$) were concordant with the marked change in body temperature.

Conclusions: The dose and type of vaccination had no effect on the time to COVID-19 negative PCR test in patients with mild COVID-19. Comparing the first dose with the booster dose, the blood glucose levels increased within the normal range. The period at which the COVID-19 nucleic acid turned negative correlated with body temperature, the proportion of lymphocytes, GOT, and serum potassium.

1. Introduction

Since early December 2019, the SARS-CoV-2-induced coronavirus disease 2019 (COVID-19) pandemic has undoubtedly caused a

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catastrophic impact worldwide [1]. The Delta and Omicron variants recently have led to a significant increase in the number of cases [2]. Globally, there have been 603,711,760 confirmed cases and 6,484,136 death cases of COVID-19 until 7 September 2022 [3]. The typical incubation period ranges from 2 to 14 days [4]. In general, the clinical symptoms and signs of COVID-19 include cough, sore throat, fever, diarrhea, headache, muscle or joint pain, fatigue, and loss of sense of smell and taste [5]. More than 80% of patients show mild or no symptoms [6,7], while approximately 5% of patients with COVID-19 show critical illness [8,9].

The time to negative PCR test (TNPT) in this study was defined as a change from a positive to a negative nucleic acid test. Numerous factors determine the TNPT and the severity of COVID-19 disease. Existing evidence indicates that vaccines offer some protection against COVID-19 [10]. This might reduce symptoms of COVID-19 infection and accelerate TNPT. COVID-19 is also a systemic infection that exerts significant impact on the metabolism [11]. Thus, a fast and convenient assessment of laboratory variables related to the speed of disease recovery turning negative has a vital significance. Biochemical indicators like serum leukocytes [12], C-reactive protein (CRP), lymphocyte, platelet, D-dimer, and so on [13,14] have been proved associated with COVID-19 outcomes. However, there are limited studies on biochemical indicators associated with the speed of COVID-19 improvement. Fever or TNPT do not indicate a more or less serious illness. The main impact of the study is the identification of biochemical markers for less time to negative PCR test and unique clinical features of mild COVID-19.

Here, based on the data during the outbreak of COVID-19 in Wuxi city in China, we integrated patient characteristics, vaccination status, related laboratory variables, and the TNPT to explore the relationship between laboratory variables and clinical features in patients with COVID-19 after non-mRNA vaccination, and tried to find the great influence of vaccination and COVID-19 infection on humans.

2. Materials and methods

2.1. Study design and patients

We performed a retrospective observational cohort study. The diagnosis of COVID-19 was set up according to China's National Health Commission criteria. COVID-19 patients in Wuxi Fifth People's Hospital from June 28, 2022, to July 24, 2022, who had been provided with non-mRNA COVID-19 vaccines were involved. Only mild-moderate patients were hospitalized and only for the purpose of isolation, so they were let go once the PCR test came back negative. All data about the patients were collected from the electronic medical records at the time the patients were accepted by the hospital.

2.2. Inclusion and exclusion criteria

The patients were laboratory-confirmed SARS-CoV-2 infection by real-time RT-PCR. The criteria for discharge were freedom from symptoms and cycle threshold (CT) values greater than 35 twice. Included subjects were older than eighteen. We excluded those who did not received at least one dose of the non-mRNA COVID-19 vaccine.

2.3. Vaccination status

Non-mRNA COVID-19 vaccines are categorized into three different types: Inactivated vaccines, adenoviral-vectored vaccines, and recombinant subunit vaccines. Among them, BBIBP-CorV (Sinopharm) and Coronavac (Sinovac) are inactivated vaccines, Ad5-nCoV CanSinoBio and KCONECAVAC are adenoviral-vectored vaccines, and Zhifei Longcom and NVSI-06-08 (CHO Cells) are recombinant subunit vaccines.

To assess the efficacy of vaccination, we divided the vaccination status into three different types: vaccination with one dose, full vaccination (two doses no matter what the commercialized types of vaccines are and the time after vaccination), and vaccination with one booster dose (three doses no matter what the commercialized types of vaccines are and the time after vaccination).

2.4. Data extraction

Age, sex, vaccination status, the severity of the fever, and biochemical parameters on admission were recorded. Specifically, low-grade fever was considered $<38\ ^{\circ}C$, moderate fever was between 38 °C and 39 °C, and high fever was defined as a temperature $\geq 39\ ^{\circ}C$. Hospital length of stay (days) was also recorded for the analysis of symptom severity.

2.5. Statistical analysis

Statistical analysis was performed with SPSS software (IBM SPSS Statistics 25). A Kruskal-Wallis test was applied in comparisons between several groups while correlations were examined with Spearman's test. Univariate linear regression was further conducted for evaluating relationships between continuous variables.

2.6. Ethics approval

This project is a retrospective study that received a waiver for informed consent. It has received ethics approval by Ethics Committee of Wuxi Ninth People's Hospital.

3. Results

3.1. Patient characteristics

In this study, a total of 228 people were included. All patients included received their last vaccination at least one month ago. Collectively, there were 133 (58.3%) males and 95(41.7%) females with a mean age of 37.7 ± 14.2 years old. All patients had a mild COVID-19 disease since they have clinical symptoms, meet the COVID-19 case definition and have no evidence of viral pneumonia or hypoxia. Sixteen (7.0%) patients had a history of hypertension while three (1.3%) of them had diabetes mellitus. Only one patient had hyperlipidemia and only one patient had a history of hepatitis. The average TNPT was 12.5 ± 2.8 days (Table 1). Of note, average COVID-19 TNPT in males was 12.3 ± 2.7, and 12.7 ± 2.8 in females. A Wilcoxon rank sum test was applied and no statically significant differences in the TNPT were found in different genders ($z = -1.532$, $P = 0.125$).

3.2. The correlation between biochemical parameters and dose of COVID-19 vaccine

Seven patients only received one dose of the vaccine, 51 were vaccinated with two doses, and 170 were vaccinated with three doses of non-mRNA COVID-19 vaccines. No one involved was unvaccinated. Of patients with one vaccine dose, four (1.8%) were injected with one dose of inactivated vaccine, and the rest three (1.3%) were injected with one dose of adenoviral-vectored vaccine. Patients vaccinated with two doses consisted of four groups (full inactivated vaccination, full adenoviral-vectored vaccination, full recombinant subunit vaccination, and full mixed vaccination). Patients vaccinated with one booster were classified into five groups: full inactivated vaccination + inactivated booster, full inactivated vaccination + adenoviral-vectored booster, full inactivated vaccination + recombinant subunit booster, full adenoviral-vectored vaccination + adenoviral-vectored booster, and full recombinant subunit vaccination + recombinant subunit booster. More details are presented in Table 2.

To investigate the interactions between average COVID-19 TNPT and vaccine doses, we conducted the Kruskal-Wallis test. It seemed the number of vaccine doses exert no effects on COVID-19 TNPT ($P = 0.559$). There was no significant difference between inactivated vaccine, adenovirus-infected vaccine and recombinant subunit vaccine in terms of mean TNPT, whether one, two or three doses were administered. (Tables S1–3).

Our analysis also proved that body temperature did not depend on the vaccine doses (Kruskal-Wallis test, $P = 0.706$) (Fig. 1A). Inflammatory indicators such as WBC ($P = 0.408$), lymphocytes ($P = 0.592$), and CRP ($P = 0.209$) were likewise not associated with vaccine doses (Fig. 1B). Other biochemical parameters including HB($P = 0.246$), platelets ($P = 0.436$), DDI ($P = 0.374$), CK ($P = 0.677$), potassium ($P = 0.466$), sodium ($P = 0.133$), chlorine ($P = 0.652$), creatinine ($P = 0.242$), glutamic-pyruvic transaminase ($P = 0.855$), glutamic oxaloacetic transaminase (GOT) ($P = 0.202$), and total bilirubin ($P = 0.568$) also did not correlate with the number of vaccines (Fig. 1C–H). Interestingly, the blood glucose levels in patients with only one dose was significantly different from three doses ($P = 0.024$), but no differences were observed in those who were full vaccination (one dose vs. full vaccination, $P = 0.223$; full vaccination vs. one booster dose, $P = 0.457$). It seemed the blood glucose levels were marginally affected by different doses but was in the normal range (Fig. 1I).

3.3. The correlation between biochemical parameters and TNPT

The correlation between the TNPT and clinical and biochemical parameters was assessed using Spearman's correlations test (Table 3). In this study, body temperature ($r = 0.168$, $P = 0.011$) and percentage of lymphocytes ($r = -0.219$, $P = 0.001$) were significantly associated with the TNPT. Linear regression results of body temperature and the percentage of lymphocytes were presented in Fig. 2A and B. Moreover, body temperature ($\beta = 0.938$, $P = 0.003$) significantly positively predicted days of serological transition, and lymphocyte percentage ($\beta = -4.24$, $P = 0.022$), creatinine ($\beta = -0.03$, $P = 0.039$), and glutamate oxaloacetate

Table 1
Patients information.

Variables	Total patients(N = 228)
Age, years	
Mean ± SD	37.7 ± 14.2
Median(range)	35.0 (5–77)
Gender	
Male	133(58.3%)
Female	95(41.7%)
Underlying diseases	
Hypertension	16(7.0%)
Diabetes mellitus	3(1.3%)
Hyperlipidemia	1(0.4%)
Hepatitis	1(0.4%)*
Average hospitalization time, days	
Mean ± SD	12.5 ± 2.8
Median(range)	13 (5–19)

* The only one patient involved had hepatitis B.

Table 2
The detail information about COVID-19 vaccinations.

Variables	Total patients(N = 228)	Average days post vaccination	Average time to negative PCR test
One dose		238.9 ± 169.4	13.0 ± 3.1
inactivated vaccines	4 (1.7%)	279.0 ± 168.7	13.5 ± 3.3
adenoviral-vectored vaccines	3 (1.3%)	185.3 ± 189.4	12.3 ± 3.2
recombinant subunit vaccines	0 (0%)	/	/
Full vaccination (two doses)		288.5 ± 88.3	12.9 ± 2.0
full inactivated vaccination	48 (21.1%)	290.0 ± 89.9	12.9 ± 2.0
full adenoviral-vectored vaccination	0 (0%)	/	/
full recombinant subunit vaccination	0 (0%)	/	/
full mixed vaccination	3 (1.3%)	265.0 ± 64.6	13.7 ± 2.9
One booster dose (three doses)		166.0 ± 59.0	12.4 ± 3.0
full inactivated vaccination + inactivated booster	160 (70.2%)	165.3 ± 53.4	12.3 ± 3.0
full inactivated vaccination + adenoviral-vectored booster	1 (0.4%)	115	11
full inactivated vaccination + recombinant subunit booster	3 (1.3%)	64.3 ± 26.7	14.3 ± 3.1
full adenoviral-vectored vaccination + adenoviral-vectored booster	2 (0.9%)	123.5 ± 12.0	15.5 ± 0.7
full recombinant subunit vaccination + recombinant subunit booster	4 (1.8%)	306.0 ± 77.2	13.5 ± 1.7

transaminase ($\beta = -0.064$, $P = 0.048$) negatively predicted days of serological transition (Table S4).

Days to negative PCR test for 14 days or more for COVID-19 disease were less common (26.3%) and there were no deaths. The mean TNPT in this study were 12.5 days. Based on this, all patients were sorted into two groups: the long stay group and the short stay group. The increase in lymphocyte percentage ($P = 0.009$) and GOT ($P = 0.025$) within the normal range are negatively related to the TNPT (Table 4).

3.4. Relationship between biochemical parameters and body temperature

Since fever was the main symptom after COVID-19 infection, correlation analysis and linear regression between body temperature and biochemical parameters were also conducted (Table S5). The percentage of lymphocytes ($\beta = -0.147$, $P = 0.026$) and the content of potassium ($\beta = -0.212$, $P = 0.001$) correlated inversely with body temperature (Fig. 3A and B).

We divided body temperature into four groups: normal temperature, low-grade fever, moderate fever, and high fever. The percentage of lymphocytes ($P = 0.007$) and serum potassium ($P = 0.004$) were concordant with the marked change in body temperature. Further information was given in Table 5.

4. Discussion

The COVID-19 pandemic continues, and the new COVID-19 cases worldwide continue to increase nowadays [15]. It is pointed out that the case fatality rate of hospitalized patients with COVID-19 is 4.3%–15% [16–18]. Rapid and effective prediction of the rate of COVID-19 TNPT will contribute to the rational allocation of medical resources. The COVID-19 vaccine is considered effective and safe in preventing serious COVID-19 infections, hospitalizations, and deaths [19]. Effective implementation of COVID-19 vaccination will help combat COVID-19. Asymptomatic and mild COVID-19 may be more common in post-vaccination COVID-19. Despite vaccine reactions, COVID-19 may occur after vaccination due to initial vaccine failure or breakthrough infection [20]. There was evidence suggesting that critical illness was inversely correlated with the number of vaccinations and was lowest in the booster vaccine group. Death and length of hospital stay were similar between various inoculation doses [21]. Interestingly, evidence also showed that COVID-19 vaccine helped to clear viral RNA in moderate cases but had no effect in patients with mild disease [22]. Hence, figuring out the impact of vaccines in mildly ill patients is critical. This paper focused on the relationship between laboratory variables and clinical features in patients with mild COVID-19 after non-mRNA vaccination. To deal with this problem, we explored the correlation between vaccine status and the TNPT. We also generated all possible biochemical parameters and tried to find the influence of vaccination and COVID-19 infection.

Non-mRNA COVID-19 vaccines include inactivated vaccines, adenoviral-vectored vaccines, and recombinant subunit vaccines. Inactivated vaccines are relatively safe; however, they induce relatively lower levels of antibodies than live attenuated and mRNA vaccines [23]. In our study, different types of non-mRNA vaccines also seemed not connected with the TNPT. We observed that non-mRNA vaccine doses did not have obvious implications on the TNPT.

The patients enrolled in our study were all more than 30 days after the final vaccination. Though most of them had taken booster vaccine doses, studies indicated that vaccine immunity might decrease over time [24]. Due to weakened vaccine efficacy, the effect of vaccination or not on the length of hospital stay was not obvious. Another reason is the patients' admission time was relatively short. In the context of the high incidence of COVID-19, hospitalizations longer than 14 days or deaths are uncommon after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in Scotland [25]. In our study, the percentage of patients hospitalized for more than 14 days was only 26.32%. The relatively short hospital stay prevents the vaccine's effects from being distinguished. Moreover, in order to prevent epidemics, whether the patient can be discharged is based on nucleic acid evidence rather than clinical symptoms. Different discharge

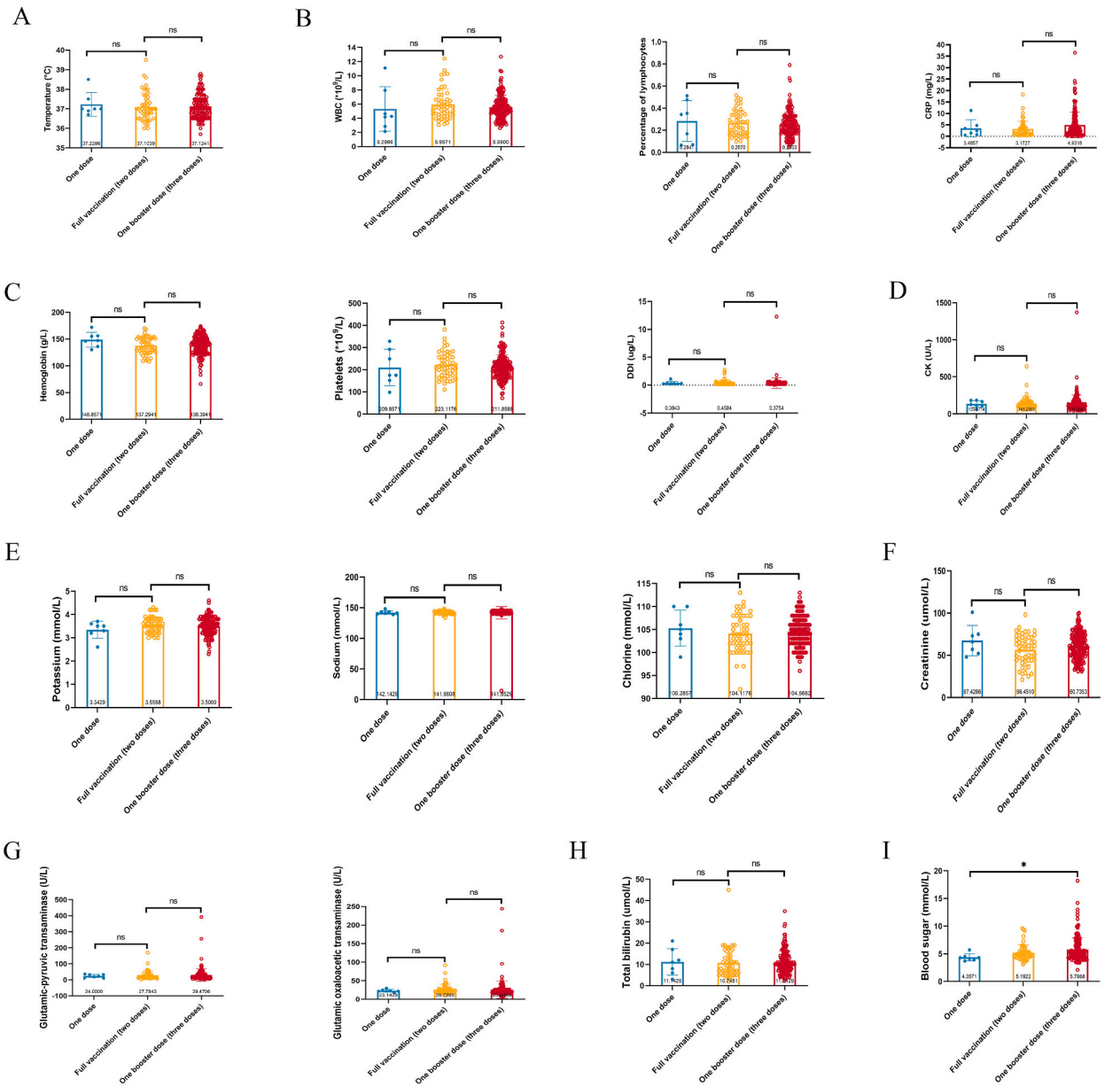

Fig. 1. The association between vaccine doses and clinical predictors like (A) body temperature (P = 0.706); (B) inflammatory indicators such as WBC (P = 0.408), lymphocytes (P = 0.592) and CRP (P = 0.209); (C) hemocytes associated parameters such as HB(P = 0.246), platelets (P = 0.436), DDI (P = 0.374); (D) CK (P = 0.677); (E) electrolytes such as potassium (P = 0.466), sodium (P = 0.133), chlorine (P = 0.652); (F) creatinine (P = 0.242); (G) glutamic-pyruvic transaminase (P = 0.855), glutamic oxaloacetic transaminase (P = 0.202), and (H) total bilirubin (P = 0.568).

standards may also be the cause of the difference. This might also cause the extension of hospital stay in our research. Although the conventional strategy of early discharge with home oxygen resulted in higher readmission rates [26], for the mildly COVID-19 patients in our study, this may also be a way to shorten hospital stays and save healthcare resources.

The inflammatory indicators, platelets, serum electrolytes, and so on were proved not to be relevant with vaccination status. Remarkably, the blood glucose levels rose within the normal range comparing the first dose with the booster dose. Since the patients we included were all with mild COVID-19 diseases and not received steroids, we excluded the glycemic effect of steroids in this situation. Several cases of COVID-19 vaccination-induced hyperglycemia were reported [27–29]. It seemed that COVID-19 vaccines were associated with the elevated blood glucose levels or the uncovering of underlying diabetes. The specific mechanism remains to be elucidated. Adrian H Heald speculated that vaccination usually triggers different levels of immune responses within and between individuals, thus having complex downstream effects on metabolism, including regulation of blood glucose levels [30]. This conjecture, however, warrants further studies.

Table 3
Correlations between the time to negative PCR test and laboratory variables.

Variables	Mean ± SD	Correlation coefficient (r)	P
Body temperature	37.1 ± 0.6	0.168	0.011
WBC	5.6 ± 1.9	−0.033	0.619
Lymphocytes	0.3 ± 0.1	−0.219	0.001
CRP	4.5 ± 5.2	0.082	0.216
HB	138.5 ± 17.5	−0.058	0.383
Platelets	214.3 ± 56.3	−0.085	0.200
DDI	0.4 ± 0.9	0.071	0.284
CK	138.6 ± 109.9	0.094	0.157
Potassium	3.5 ± 0.4	0.075	0.257
Sodium	141.9 ± 8.7	−0.112	0.092
Chlorine	104.5 ± 3.4	−0.106	0.111
Creatinine	60.0 ± 16.2	−0.098	0.141
Glutamic-pyruvic transaminase	28.9 ± 35.4	−0.076	0.254
Glutamic oxaloacetic transaminase	25.8 ± 21.3	−0.098	0.139
Total bilirubin	11.0 ± 5.8	0.016	0.811
Blood sugar	5.3 ± 2.0	0.052	0.432

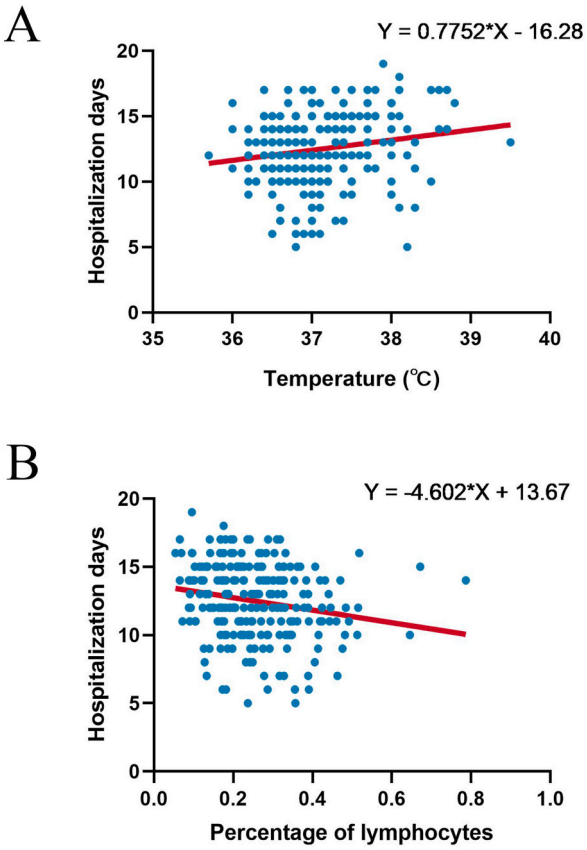

Fig. 2. Linear regression results of (A) body temperature and (B) percentage of lymphocytes with the time to negative PCR test.

Body temperature, percentage of lymphocytes and GOT were related to the TNPT, which is also the length of hospitalization stays in our research. In the pediatric population, absolute lymphocyte count decreases with disease severity [31]. We also found that increase in the percentage of lymphocytes in the normal range is associated with a decrease in the length of hospital stay. The main reason is that cellular immunity plays an important role in limiting the severity of disease and solving infection, especially in $CD4^+$ T helper cells [32]. Some studies have found that severe patients with COVID-19 were suggested to have higher levels of GOT than non-severe patients [17,33–35]. Preethi Ramachandran et al. suggested no prolonged mortality or length of stay in patients with elevated transaminases [36]. Intriguingly, we observed that increase in glutamate oxaloacetate aminotransferase in the normal range was associated with a decrease in length of stay. We speculated that this phenomenon was linked to immunity and the inflammatory

Table 4
Related factors affecting the time to negative PCR test.

Variables	Short stay group	Long stay group	Mann-Whitney u Test P value
WBC	5.7 ± 1.7	5.6 ± 2.0	0.38
Lymphocytes	0.3 ± 0.1	0.2 ± 0.1	0.009
CRP	4.7 ± 5.9	4.4 ± 4.6	0.523
HB	140.3 ± 18.2	136.8 ± 16.7	0.052
Platelets	218.9 ± 50.4	209.0 ± 60.8	0.111
DDI	0.4 ± 1.2	0.4 ± 0.3	0.119
CK	141.4 ± 137.5	134.9 ± 74.2	0.374
Potassium	3.5 ± 0.4	3.5 ± 0.4	0.668
Sodium	142.7 ± 2.0	141.1 ± 12.1	0.077
Chlorine	104.8 ± 3.4	104.2 ± 3.5	0.260
Creatinine	61.8 ± 15.1	58.4 ± 17.0	0.051
Glutamic-pyruvic transaminase	32.9 ± 44.7	25.2 ± 22.8	0.121
Glutamic oxaloacetic transaminase	28.4 ± 27.3	23.4 ± 12.8	0.025
Total bilirubin	10.8 ± 5.3	11.3 ± 6.2	0.87
Blood sugar	5.5 ± 1.9	5.7 ± 2.2	0.274

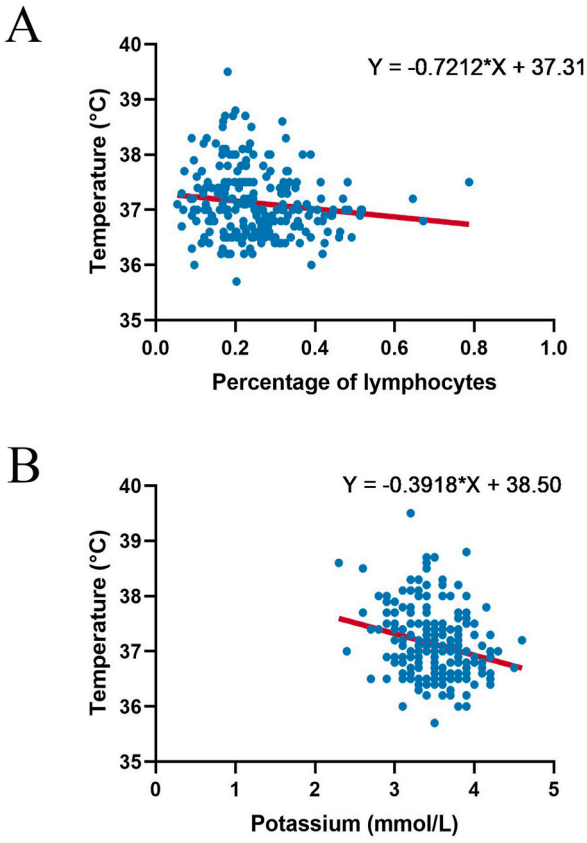

Fig. 3. Linear regression results of (A) the percentage of lymphocytes and (B) the content of potassium with body temperature.

response. Reasons for this need further investigation.

We also found that the percentage of lymphocytes and serum potassium were consistent with the significant changes in body temperature. Electrolyte imbalance can be used as a marker of poor prognosis for COVID-19 [37]. Data from Jiangtao Yin et al. showed patients with hypokalemia are more likely to have prolonged TNPT and days of hospitalization [38]. The serum potassium might affect body temperature and thus extended time in hospital for symptomatic treatment. However, since we did not observe the relationship between serum potassium and the TNPT, the conclusion that hypokalemic patients are more likely to have longer TNPT and longer days of hospitalization and the mechanisms involved remain to be investigated.

Table 5
Relationship between biochemical parameters and body temperature.

Variables	Normal temperature	Low grade fever	Moderate fever	High fever	Kruskal-Wallis test P value
WBC	5.6 ± 1.9	5.8 ± 1.8	5.4 ± 1.8	7.3	0.501
Lymphocytes	0.3 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.18	0.007
CRP	4.0 ± 4.8	4.8 ± 5.5	7.1 ± 6.1	3.1	0.170
HB	138.2 ± 17.8	140.3 ± 17.4	132.4 ± 15.4	126	0.213
Platelets	217.2 ± 55.2	213.5 ± 56.5	199.3 ± 65.3	199	0.425
DDI	0.4 ± 0.4	0.5 ± 1.3	0.3 ± 0.1	0.27	0.822
CK	139.9 ± 133.4	133.6 ± 71.4	155.9 ± 82.7	98	0.674
Potassium	3.6 ± 0.4	3.4 ± 0.4	3.3 ± 0.4	3.2	0.004
Sodium	141.5 ± 11.7	142.5 ± 2.1	141.8 ± 2.1	141	0.311
Chlorine	104.7 ± 3.1	104.4 ± 3.8	104.0 ± 3.8	102	0.577
Creatinine	58.2 ± 16.2	62.8 ± 16.0	58.9 ± 16.3	58	0.338
Glutamic-pyruvic transaminase	30.0 ± 39.2	26.3 ± 29.7	29.5 ± 28.7	103	0.339
Glutamic oxaloacetic transaminase	25.9 ± 22.8	24.7 ± 19.2	27.4 ± 18.5	71	0.348
Total bilirubin	10.8 ± 4.7	11.2 ± 7.0	12.3 ± 5.7	6	0.444
Blood sugar	5.4 ± 1.6	5.9 ± 2.6	5.3 ± 1.3	4.9	0.780

4.1. Study strengths and limitations

Our study has several limitations. First, this study was a single-center study. Our samples were limited to only one hospital in Wuxi, China. Secondly, more evidence needed to be gathered to confirm the rationale behind the phenomena we found. Furthermore, no follow-up data were obtained because the follow-up time was not long enough. The long-lasting effects of the COVID-19 pandemic are still not fully known.

Nevertheless, our findings highlight the associations between laboratory variables and clinical features. We focused on the relatively safer non-mRNA vaccines. In order to lessen the burden on the medical system, we also identify clinical determinants of COVID-19 TNPT in this research. And the potential mechanisms will be examined in future studies.

5. Conclusions

The dose and type of vaccination did not affect the TNPT in patients with mild COVID-19. The blood glucose levels rose within the normal range comparing the first dose with the booster dose. Body temperature, the percentage of lymphocytes, GOT, and serum potassium were related to the TNPT.

Author contribution statement

Dan Zhu and Zuliang Min: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Xiao Yu and Yanxiaoqian Chen: Performed the experiments.

Tao Zhou, Yating Liu and Lu Liu: Analyzed and interpreted the data.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e18167.

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