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Patterns and Changes in the Treatment of Patients with Type II Diabetes Mellitus in Egypt: The DISCOVER Program

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Abstract

The DISCOVER study is a three-year, non-interventional prospective study conducted in 37 countries, including Egypt, to assess the treatment patterns and outcomes in patients with type 2 diabetes mellitus initiating a second-line antidiabetic therapy (add-on or switch). In this report of the Egyptian cohort of DISCOVER, baseline data were collected according to routine clinical practice at 38 study sites, using a standardized electronic case report form, in the period from December-2014 to November-2019. We enrolled 583 patients (mean age: 52.9 ± 9.8 years and median duration since diagnosis: median 36.5, IQR 18.1, 70.4 months). The mean HbA1c value at baseline was 8.6 ± 1.4%, indicating poor glycemic control. The most commonly prescribed first-line medications were metformin or sulfonylurea monotherapy. For second line-therapy, the majority of patients switched to dual therapy with metformin plus sulfonylureas or DPP-4 inhibitors. Fewer patients switched to triple therapy, treatment by four or more medications, or insulin treatment (15, 12, and 35 patients, respectively). The most commonly cited reasons for switching to second-line therapy were lack of efficacy, weight gain, hypoglycemic events, and side effects (549, 54, 25, and 21 patients, respectively). The set treatment target of enrolled patients at the initiation of second-line therapy was an HbA1c level of 6.9%. Follow-up data will assess the outcomes of such changes in the Egyptian population.

Keywords

Diabetes Mellitus, Glucose Control, Metformin, Patient-Reported Outcomes, Egypt, HbA1c, Medication

1. Introduction

Approximately 420 million individuals worldwide have type 2 diabetes mellitus (T2DM). This prevalence is expected to reach 642 million individuals by 2040 [1] [2]. The International Diabetes Federation (IDF) classifies Egypt as the ninth leading country in terms of T2DM prevalence (around 15% of the adult Egyptian population), with an estimated annual mortality of 86,478 [3] [4]. Additionally, as many as 40% of T2DM patients in Egypt remain undiagnosed [3]. Due to its macrovascular and microvascular complications, T2DM remains the leading cause of retinopathy and vision loss, peripheral neuropathy, chronic nephropathy, and leg amputation in Egypt [5] [6].

Recent guidelines from the American Diabetes Association (ADA) and the American College of Endocrinology recommend tight glucose control (HbA1c < 7%) for newly-diagnosed patients with T2DM and those with long life expectancy [7] [8]. These guidelines are based on the results of long-term studies that showed reduced mortality and reductions in cardiovascular and microvascular complications when glucose levels are tightly controlled [9] [10]. Both ADA and The European Association for the Study of Diabetes (EASD) recommend metformin (MET) added to lifestyle modifications as the first-line glucose-lowering therapy in patients with T2DM. If MET monotherapy fails to adequately control HbA1c levels, guidelines recommend adding a second glucose-lowering agent, but few clearly state optimal treatment pathways [7] [8].

Understanding the real-life patterns and outcomes of T2DM treatment is essential to aid in developing new strategies aimed at optimal blood glucose control. For example, previous studies have shown sub-optimal adherence to glucose-lowering treatment as a barrier to achieving glycemic target among Egyptian diabetic patients. They also concluded that the number of prescribed medications, the therapeutic regimen's complexity, and the treatment costs negatively affect the adherence rates [11] [12].

We have no recent studies about the treatment patterns and outcomes in patients with T2DM in Egypt to the best of our knowledge. The DISCOVER study is a three-year, non-interventional, prospective study, conducted in 37 countries, including Egypt (NCT02322762), to assess the pharmacological patterns (first- and second-line therapy) and outcomes (level of glycemic control) in patients with T2DM who are initiating second-line glucose-lowering therapy. Here we report the baseline characteristics (including HbA1c values) of the enrolled Egyptian patients and the reasons for changing their first-line antidiabetic treatments.

2. Methods

2.1. Study Design and Population

The DISCOVER study is a prospective, multi-national study performed in 37 countries, including Egypt. We enrolled an average of 15 patients per center from 38 centers (including 36 primary health care centers). These centers had specialty care, electronic medical records, and an adequate flow of T2DM patients (>50 patients/month). The predominant mode of referral to these centers was from primary care clinics. In Egypt, the study was conducted in the period of December-2014 to November-2019.

2.2. Inclusion and Exclusion Criteria

In this study, patients were enrolled if they were aged > 18 years, diagnosed with T2DM, and were initiating a second-line antidiabetic treatment (add-on or switch). We excluded patients with T1DM, pregnant women, patients with a renal transplant or undergoing dialysis, and patients whose first-line treatment was either insulin (or another injectable agent) or herbal remedies and natural medicines alone.

2.3. Study Variables

Baseline data were collected according to routine clinical practice at each site, using a standardized electronic case report form. Baseline variables recorded included: demographic and physiological parameters, treatment options and reasons for treatment change, individualized HbA1c targets set by physicians, and laboratory test results, including HbA1c level, when available. We assessed the health status of enrolled patients using the Short-Form 36 (SF-36) version 2 questionnaire. The main endpoints in this report are the level of glycemic control (HbA1c) at baseline, the proportions of patients using different antidiabetic regimens and medications, and the reasons for changing to second-line treatments.

2.4. Sample Size Calculation and Statistical Analysis

The multinational DISCOVER study in 37 countries, including Egypt, has an estimated overall sample size of 11,100 patients based on the four criteria mentioned in Ji L *et al.* (2017). These criteria are a minimum of 200 patients in any subgroup of patients, at least 200 patients meeting each of the composite endpoints of macrovascular and microvascular complications, at least 200 patients meeting each macrovascular and microvascular endpoint at year 3, and an estimated attrition rate of 15% per year of follow-up [13].

Categorical data were presented as frequencies and percentages, while continuous data were presented as means ± standard deviations, as well as medians and interquartile ranges (IQR). All presented statistical analyses were carried out using SAS (version 9.2; SAS Institute Inc., Cary, NC, USA). For some outcomes, data were not available from all patients; therefore, patients with missing data

were excluded from the analysis.

3. Results

3.1. Baseline Patient Characteristics

The mean age of the enrolled 583 patients was 52.9 ± 9.8 years. The majority of patients in our sample were male (56.6%). The mean BMI was 31.8 ± 5.1 kg/m^2, and 115 patients were current smokers or ex-smokers (91 and 24 patients, respectively). At baseline, the mean values of blood glucose measures indicated poor glycemic control: HbA1c (8.6% ± 1.4%), fasting plasma glucose (182.8 ± 53.7 mg/dL), and post-prandial blood glucose (257.3 ± 70.4 mg/dL). About 36% of patients had hypertension, and 25.9% had hyperlipidemia. However, the mean values of lipid profile components (total cholesterol, triglycerides, LDL, and HDL) were within or near the normal ranges (Table 1).

Table 1. (a) Baseline demographic characteristics, vital signs and lab values in enrolled patients; (b) Vital signs and lab values in enrolled patients.

(a)

	Total (N = 583)
Age (years)	
Mean ± SD	52.9 ± 9.8
Median (IQR)	53.0 (46.1, 59.1)
Gender	
Male	330 (56.6)
Female	253 (43.4)
BMI (kg/m^2)	
Mean ± SD	31.8 ± 5.1 (527)
Median (IQR)	31.1 (28.1, 34.6)
Waist circumference (cm)	
Mean ± SD	104.5 ± 24.3 (337)
Median (IQR)	105 (96, 120)
Self-reported ethnicity	
Caucasian	35 (6)
Arabic	548 (94)
Living arrangement status	
Lives alone	14/564 (2.5)
Does not live alone	548/564 (97.2)
Declined to answer	2/564 (0.4)
Education level	
No formal education	19/558 (3.4)
Primary (1 - 6 years of education)	63/558 (11.3)

Continued

Secondary (7 - 13 years of education)	172/558 (30.8)
University/Higher Education (13+ years)	304/558 (54.5)
Main working status	
Employed	319/572 (55.8)
Self-Employed	46/572 (8)
Disabled	1/572 (0.2)
Not working	162/572 (28.3)
Retired	44/572 (7.7)
Tobacco Smoking	
Non-smoker	458/573 (79.9)
Ex-smoker	24/573 (4.2)
Current smoker	91/573 (15.9)

Data are number (%) for categorical outcomes or mean ± standard deviation and median (IQR) for continuous outcomes. BMI: Body mass index.

(b)

	Total (N = 583)
Systolic BP (mm. Hg)	
Mean ± SD	133.0 ± 14.9 (555)
Median (IQR)	130 (120, 140)
Diastolic BP (mm. Hg)	
Mean ± SD	82.8 ± 8.6 (555)
Median (IQR)	80 (80, 90)
Pulse rate at rest (bpm)	
Mean ± SD	78.4 ± 6.8 (583)
Median (IQR)	80 (74, 82)
HbA1C (%)	
Mean ± SD	8.6 ± 1.4 (543)
Median (IQR)	8.4 (7.9, 9.1)
Fasting Glucose (mg/dL)	
Mean ± SD	182.8 ± 53.7 (543)
Median (IQR)	177 (149, 208)
Random Glucose (mg/dL)	
Mean ± SD	250.6 ± 59.9 (113)
Median (IQR)	250 (206, 297)
Post Prandial Glucose (mg/dL)	
Mean ± SD	257.3 ± 70.4 (501)
Median (IQR)	249 (213, 295)
HDL (mg/dL)	
Mean ± SD	43.6 ± 9.6 (218)

Continued

Median (IQR)	42 (38, 49)
LDL (mg/dL)	
Mean ± SD	124.3 ± 37.9 (227)
Median (IQR)	125 (95, 154)
Total Cholesterol (mg/dL)	
Mean ± SD	201.6 ± 45.1 (264)
Median (IQR)	200 (170, 230.5)
Triglycerides (mg/dL)	
Mean ± SD	164.5 ± 81.6 (258)
Median (IQR)	150 (112, 189)

Data are mean ± standard deviation and median (IQR) for continuous outcomes for continuous outcomes. **BP:** blood pressure, **HDL:** High-density lipoprotein, **LDL:** Low-density lipoprotein.

At the start of this study, the duration of T2DM since diagnosis was 49.2 ± 44.3 (median 36.5, IQR: 18.1, 70.4) months. The majority (n = 508, 87.1%) have the diagnose of T2DM following the appearance of diabetes-related symptoms, while only 61 (10.5%) and 14 (2.4%) have that diagnosis upon routine monitoring or referral, respectively. The most common macrovascular complication was coronary artery disease (7.5%), while the most common microvascular complications were peripheral neuropathy (14.8%) and erectile dysfunction (5%). The most commonly used medications for other conditions were antihypertensive (38.8%), lipid-lowering medications (33.8%), and antiplatelet medications (17.5%). Our results showed impairments in all measured health status domains (average below 50), according to SF-36v2.

3.2. First-Line Antidiabetic Treatments

At the baseline, the majority of patients 435 (74.6%) were on monotherapy, predominantly receiving metformin (234 patients) or sulfonylurea (193 patients). Only 137 patients (23.5%) were receiving dual therapy, mainly in the form of metformin plus sulfonylureas or DPP-4 inhibitors. Overall, ten patients received triple therapy. Nine of them received triple therapy containing metformin and sulfonylureas plus DPP-4 inhibitors or thiazolidinediones in our sample, as shown in Table 2.

3.3. Second-Line Antidiabetic Treatments

The mean time from diagnosis to the initiation of second-line therapy was 5.6 years. The majority of patients (n = 361, 62%) were shifting to dual therapy, mainly in the form of metformin plus DPP-4 inhibitors (27.5%) or sulfonylureas (25.6%). One hundred twenty-one patients (20.7%) initiated triple therapy, mainly in the form of metformin and Sulfonylureas plus DPP-4 inhibitors or thiazolidinediones. Only 12 and 35 patients switched to ≥four drugs or insulin (with or without oral medications), respectively (Table 2).

Table 2. First and second line treatment medications in the enrolled sample.

	Total (N = 582)	
	First Line Class	Second Line Drugs
Monotherapy		
Met	234 (40.2%)	12 (2.1%)
SU	193 (33.2%)	11 (1.9%)
DPP4	4 (0.7%)	25 (4.3%)
Other	4 (0.7%)	5 (0.9%)
Dual Therapy		
Met + SU	103 (17.7%)	149 (25.6%)
Met + DPP4	24 (4.1%)	160 (27.5%)
Met + other	3 (0.5%)	10 (1.7%)
SU + Thiaz		10 (1.7%)
Other Dual therapy	7 (1.2%)	32 (5.5%)
Triple Therapy		
Met + SU + DPP4	6 (1.0%)	85 (14.6%)
Met + SU + Thiaz	3 (0.5%)	21 (3.6%)
Other Triple therapy	1 (0.2%)	15 (2.6%)
4 or 4+ Therapy		12 (2.1%)
Insulin (May also receive oral therapy)		35 (6.0%)

3.4. Reasons Underlying Treatment Changes

The most common reason for changing first-line medications was lack of efficacy (n = 549 patients; 94.2%). Less common reasons included weight gain, the occurrence of hypoglycemic events, and side effects (9.3%, 4.3%, and 3.6%, respectively). Second-line therapy was started to achieve higher efficacy, tolerability, and to avoid both weight gain and hypoglycemic events (87.1%, 32.6%, 26.1%, and 22.3%, respectively). Seeking more affordable cost was mentioned as a reason for selecting second-line treatments in 48 patients (8.2%) (Table 3). At the initiation of second-line treatment, a target HbA1c goal was set for 447 (76.7%) patients. The mean target HbA1c was 6.9% ± 0.4%. Physicians reported few restrictions on prescribing the majority of available drugs to the study patients. However, physicians reported restrictions in prescribing alpha-glucosidase, acarbose, and rosiglitazone for 70 (12%), 62 (10.6%), and 43 (7.4%) patients, respectively.

4. Discussion

The DISCOVER study program was established to improve understanding of the treatment patterns and outcomes of patients with T2DM at the global level. In this report of the DISCOVER baseline data from Egypt, we present the treatment patterns of patients with T2DM, for which data have been scarce on this so far.

Table 3. Changing first-line therapy and switching to second-line therapy

	Total (N = 583)
Consult Setting	
Inpatient	10/558 (1.8%)
Outpatient	548/558 (98.2%)
Hospitalization for facilitating diabetes treatment change	3/547 (0.5%)
Reason for changing First Line Therapy	
Lack of Efficacy	549 (94.2%)
Hypoglycemic Event	25 (4.3%)
Weight Gain	54 (9.3%)
Side Effect	21 (3.6%)
Developed Acute Disease	2 (0.3%)
Developed Chronic Disease	2 (0.3%)
Affordability	0 (0.0%)
Inability to Self-administer	5 (0.9%)
Patient Request	13 (2.2%)
Poor adherence	17 (2.9%)
Patient convenience	7 (1.2%)
Prescriber access reasons	1 (0.2%)
Drug interaction	0 (0.0%)
Physician preference	9 (1.5%)
Reason for Choosing a Second-Line Therapy	
Efficacy	508 (87.1%)
Tolerability	190 (32.6%)
Weight	152 (26.1%)
Hypoglycemic	130 (22.3%)
Patient request	28 (4.8%)
Convenience	37 (6.3%)
Access Reason	4 (0.7%)
Cost	48 (8.2%)
Other	9 (1.5%)

We noted several significant findings. At baseline, the mean HbA1c value was 8.6%, which indicates poor glycemic control. High HbA1c levels are correlated with a higher incidence of vascular complications [14] [15]. The low percentage (9.8%) of macrovascular complications in this study may not reflect the real picture; such underestimation may be due to the lack of resources for performing investigations like electrocardiogram (ECG) and echocardiography in Egypt. The mean target aim for HbA1c in enrolled patients at the initiation of second-line treatment was 6.9%. That is in accordance with the recent guidelines that rec-

ommended setting treatment goals for HbA1c below 7% [7] [8]. These guidelines are based on the results of several studies that showed that keeping HbA1c below 7% significantly reduces the incidence of macrovascular and microvascular complications [9] [10].

The most common medication used as a first-line antidiabetic treatment in our study was metformin. This is in accordance with the current NICE and ADA guidelines [7] [16]. Moreover, the most common second-line therapy was dual therapy, mainly metformin plus SU or DPP-4 inhibitors. That reflects good adherence to international guidelines by Egyptian physicians treating patients with T2DM. In our exclusion criteria, we excluded patients whose first-line treatment included insulin or any other injectable agent. During treatment intensification, 35 patients (6%) switched to insulin (with or without oral medications). A former observational study of 51,771 patients showed that physicians were reluctant to prescribe injectable agents [17].

The most common reason for changing first-line antidiabetic therapy was lack of efficacy, and the most common reason for transitioning to second-line therapy was seeking better glucose control. That agrees with previous studies that showed that high HbA1c levels were the main driver behind switching to second-line antidiabetic therapy [18] [19]. The occurrence of side effects or hypoglycemic attacks was a less common reason for treatment changes. A former study by *Asche et al.* (2008) showed that adverse events did not significantly affect glycemic control but increased the rates of switching drugs, especially for patients on metformin or sulfonylureas [20]. Our results showed that weight gain was a relatively common adverse event that led to shifting to second-line treatments in 54 (9.3%) patients. Although previous studies have shown sub-optimal adherence among Egyptian DM patients [11] [12], in this study, it was not a common reason for shifting treatments (only cited in 17 cases).

Another interesting finding in our study was the small proportion of patients diagnosed with T2DM through regular blood glucose screening. That highlights the need for increasing the exerted efforts towards public education and awareness about the value of continuous blood glucose screening, especially in high-risk patients. Moreover, the prevalence of comorbidities like hypertension and hyperlipidemia (as indicated by the frequency of receiving concomitant medications for these conditions) was relatively high in the enrolled Egyptian patients. Therefore, multidisciplinary medical management and considering the presence of these comorbidities while prescribing antidiabetic medications is necessary.

Our study analyzed data from a relatively sizeable Egyptian population. Further, we attempted to evaluate the patient-reported outcomes, as well as the quality of life in Egyptian patients with T2DM. The study went further to determine the restrictions faced by physicians in prescribing various hypoglycemic medications. Our prospective analysis after collecting of follow-up data will focus on the outcomes of second-line treatments and provide further guidance for physicians on the optimal treatment options for Egyptian diabetic patients. More-

over, it will present data on the factors associated with prescribing specific treatments and the variations in diabetology practice across different countries.

One advantage of this current study was that it had a relatively enough sample from different centers all over Egypt; hence, it represented the overall population of people with T2DM well. However, the study's main limitation was its observational nature with some variables that could be exposed to recall bias.

5. Conclusion

In conclusion, this study showed poor glycemic control among Egyptian patients with T2DM initiating second-line treatment. Therefore, the lack of efficacy was the most common reason for changing first-line treatments. Dual therapy in the form of metformin plus Sulfonylureas or DPP-4 inhibitors was the most commonly prescribed second-line treatment. Follow-up data will assess the outcomes of such changes in the Egyptian population.

Compliance with Ethical Standards

Conflicts of Interest

All first seven authors were or are members of the DISCOVER Scientific Committee.

In addition, all first seven authors have received honoraria and research grants from Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Sharp & Dohme, Novartis, Novo Nordisk, Janssen, and Sanofi.

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Ethical Approval

ClinicalTrials.gov identifiers: NCT02322762 (DISCOVER) and NCT02226822 (J-DISCOVER).

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Stroke as a Presenting Feature of COVID-19

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Abstract

Objective: To analyze the coronavirus disease-2019 (COVID-19) patients presenting with acute stroke by determining their clinical characteristics, hospitalization course and prognosis. The common and conventional stroke risk factors in these patients were assessed with the aim of determining the role and contribution of the COVID-19 infection to stroke pathogenesis. **Methods:** Retrospective observational study involving 24 patients from a single tertiary care center over a time period of three months. Risk factors such as Age, Hypertension, Diabetes Mellitus, smoking status and underlying cardiac history were analyzed. COVID-19 relevant laboratory and radiological data were documented. **Results:** 87.5% of patients had ischemic stroke, with 58.3% of total patients being younger than 55 years. An equal incidence of both Diabetes Mellitus and Hypertension (37.5%) was identified. 29.2% were completely asymptomatic for COVID-19, of which 85.7% had no chest X-ray changes on admission. Eight patients (61.5%) developed pneumonia during admission despite an initially normal chest X-ray. **Conclusion:** Patients without COVID-19 symptoms and with normal chest radiography presenting with stroke does not rule out a possible underlying COVID-19 infection. Such patients may be positive for the virus and may go on to develop pneumonia shortly after suffering from strokes. This could suggest that stroke in COVID-19 patients is a possible initial presenting feature and consequence of the inflammatory state triggered by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection. It is imperative to analyze the association of COVID-19 and stroke, and to maintain a high index of suspicion of COVID-19 infection in stroke patients, to enhance early detection and reduce transmission.

Keywords

COVID-19, Coronavirus, Stroke, Hypercoagulable, UAE

1. Introduction

Stroke is a well-studied clinical entity and a significant cause of mortality and

morbidity, with well-recognized risk factors contributing to its pathogenesis. The Coronavirus disease of 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) is primarily a respiratory illness but multisystem involvement is being increasingly reported, including neurological system. A spectrum of neurological symptoms in COVID-19 patients including dizziness, headache and impairment of taste and smell has been demonstrated, with 5.7% of patients with severe infection and 0.8% with mild disease reporting acute cerebrovascular accidents [1]. Case series from New York [2] and Dubai, United Arab Emirates [3] have also reported stroke as a presenting feature of COVID-19. We report another series from the same center in Dubai with a different perspective to carry forward our interest in COVID-19 patients presenting with acute stroke.

Through this study, we aim to analyze COVID-19 patients presenting with acute stroke by determining their clinical characteristics, hospitalization course and outcome, and to evaluate the contribution of the conventional risk factors in causing stroke in these patients.

2. Methods

2.1. Study Design

This was a retrospective observational study from a single tertiary center caring for COVID-19 patients. Data was collected from the electronic medical records system during July-September 2020. The study was comprised of 24 patients admitted with a diagnosis of acute stroke and found to be COVID-19 positive within 24-48 hours of admission; over a time period of three months (July-September, 2020). Patients were included on the basis of World Health Organization (WHO) case definition of COVID-19 [4] with laboratory confirmation of SARS-CoV-2 by real-time polymerase chain reaction (RT-PCR) of nasopharyngeal swabs or endotracheal aspirates. Excluded participants were COVID-19 positive patients who developed a stroke 48 hours or more after admission and stroke patients who underwent thrombolysis or thrombectomy shortly after presenting. Stroke was defined on the basis of clinical presentation and imaging studies such as computed tomography of the brain.

2.2. Study Variables

Risk factors such as Age, Hypertension, Diabetes Mellitus, smoking status and underlying cardiac history were analyzed to determine their contribution to stroke pathology. These risk factors in particular were selected as they are known to influence the occurrence of strokes in individuals. In addition to classic stroke symptoms, presence of any pre-existing COVID-19 features were also recorded. Laboratory data including markers of inflammation and pro-thrombotic state such as C-reactive protein (CRP), D-Dimer, Ferritin, Lactate Dehydrogenase (LDH) and Liver enzymes, and radiological data were documented. COVID-19 related and stroke-related complications during hospital stay were analyzed to provide a better reflection of patient outcome.

3. Standard Protocol Approvals, Registrations and Patient Consents

This study was carried out in Rashid Hospital, Dubai, UAE and approved by the Dubai Ethical and Research Committee.

Data Access Statement

The data underlying this research paper was obtained with the permission of the ethical committee of Dubai Health Authority and cannot be made openly available due to confidentiality reasons. All relevant data supporting the study can be found in this paper.

4. Results

Out of the 24 patients who presented with stroke, 87.5% were ischemic (70.8% thrombotic and 16.6% embolic), while 12.5% were hemorrhagic strokes. The mean age was 53 years with a range of 30 - 77 years. 58.3% of patients were younger than 55 years, but had at least one other known contributory factor for stroke. 66.6% had dyslipidemia, 37.5% had hypertension and/or Diabetes Mellitus. Only one patient had no known stroke risk factors.

58.3% of the patients had elevated Procalcitonin (PCT) and D-dimer, while 45.8% had a raised CRP and 25% had ferritin levels above 300 ng/mL. 29.2% of the patients presented solely with stroke features and reported no prior COVID-19 symptoms. 45.8% of the patients had abnormal chest x-rays on admission, showing either consolidations or infiltrates. Eight patients, with normal chest X-ray on admission developed pneumonia during admission. Average duration of hospital stay was 15 days with 75% of patients demonstrating improvement in clinical status and 4 patients died due to COVID-19 related complications.

Table 1 compares our study population in terms of socio-demographics and stroke risk factors. Amongst both sets of patients in the table, most patients were males from the Indian subcontinent and overweight. The main differences between the two groups of patients shown in the table was that patients who presented without initial pneumonia had much less past history of smoking and less

Table 1. Socio-demographics and risk factors.

	Pneumonia on initial CXR 11 total patients (as a % of pneumonia patients)	No Pneumonia on initial CXR 13 total patients (as a % of patients without pneumonia)
Mean Age	56 years	50 years
Sex		
Male	9 (81.8%)	12 (92.3%)
Female	2 (18.2%)	1 (7.7%)
Nationality		
From the Indian Subcontinent (India/Pakistan/Bangladesh)	8 (72.2%)	10 (76.9%)

Continued

Philippines	2 (18.2%)	1 (7.7%)
Other nationalities	1 (9.1%)	2 (15.4%)
	Stroke Risk Factors	
Body mass index (BMI) less than 25	**2 (18.2%)**	**6 (46.2%)**
BMI more than/equal to 25	**9 (81.8%)**	**7 (53.8%)**
Diabetic	6 (54.5%)	2 (15.4%)
Hypertensive	**5 (45.5%)**	**6 (46.2%)**
Dyslipidemic	8 (72.7%)	8 (61.5%)
Ischemic heart disease patient	2 (18.2%)	2 (15.4%)
Current/Previous smoker	1 (9.1%)	3 (23.1%)
Never smoker	4 (36.4%)	8 (61.5%)
Previous stroke patient based on CT	2 (18.2%)	5 (38.5%)
No risk factors for stroke	0	1 (7.7%)

Table 2. The clinical characteristics, laboratory and radiological parameters of patients with and without pneumonia on admission.

	Pneumonia on initial CXR **11 total patients** **(as a % of pneumonia patients)**	**No Pneumonia on initial CXR** **13 total patients** **(as a % of patients without pneumonia)**
Most common symptoms prior to stroke		
Fever	4 (36.4%)	1 (7.7%)
Cough	4 (36.4%)	1 (7.7%)
Dyspnea	2 (18.2%)	1 (7.7%)
No prior symptoms suggesting infection **(asymptomatic COVID-19)**	1 (9.1%)	6 (46.2%)
Treated with COVID-19 targeted therapy	10 (90.9%)	7 (53.8%)
	Chest X-Ray	
Abnormal CXR on admission - had either infiltrations or consolidations	11 (100%)	0
New pneumonia developed during admission - admitted with normal CXR	0	8 (61.5%)
	Laboratory Findings	
Elevated white blood cells (WBCs)	2 (18.2%)	2 (15.4%)
Elevated PCT	7 (63.6%)	7 (53.8%)
Elevated CRP	7 (63.6%)	4 (30.8%)
High platelet count	1 (9.1%)	0
Low platelet count	0	2 (15.4%)
Elevated ferritin	3 (27.3%)	3 (23.1%)
Elevated D-dimer	6 (54.5%)	8 (61.5%)
Elevated prothrombin time (PT)	11 (100%)	12 (92.3%)
Elevated activated partial thromboplastin time (APTT)	1 (9.1%)	1 (7.7%)
International normalized ratio (INR)	3 (27.3%)	4 (30.8%)

diabetes. Table 2 compares the clinical characteristics, laboratory and radiological parameters of our study population. Many of the participants between both groups had elevated inflammatory markers and almost every single patient had an elevated prothrombin time. Additionally, the majority of patients who had pneumonia on presentation gave prior history of symptoms suggesting possible infection. Furthermore, even though most of our patients did not present with pneumonia on initial chest X-ray, more than half of these patients went on to develop pneumonia during hospital admission.

5. Discussion

Inflammatory conditions including acute respiratory infections are well-recognized triggers of cardiovascular events and stroke, and SARS-CoV-2 may act as a precipitating factor producing a pro-coagulant state either by inflammation, inducing a state of dehydration, development of antiphospholipid antibodies or due to large vessel vasculitis [5] [6].

Cardiovascular and cerebrovascular diseases share the same set of risk factors, and are important prognostic factors for poor outcome in COVID-19 infections [7]. South Asians have a higher risk of stroke compared to Whites with a younger age of onset and higher incidence of atherosclerotic risk factors such as Diabetes Mellitus and Hypertension [8]. Hypertension is also one of the five risk factors accounting for more than 80% of the global risk of all strokes [9]. Only 38% of our patients were known to be hypertensive, with all except one taking anti-hypertensives. The absence of lacunar infarcts (87%), small vessel changes (71%) or features of left ventricular hypertrophy on electrocardiogram (EKG) (87.5%) in the rest of the patients suggest the absence of chronic undiagnosed hypertension in these patients, that otherwise could have been considered as the underlying risk factor. Although age is one of the well-recognized conventional risk factors for stroke, more than half of the patients in our study were below the age of 55. Other relevant stroke risk factors such as Diabetes Mellitus and Dyslipidemia were noted in 37.5% and 66.6% of patients respectively.

Stroke-related symptoms such as motor weakness (83.3%) and speech impairment (70.8%) were the primary reason that led to our patients seeking medical attention, and SARS-CoV-2 was then diagnosed, in-hospital by RT-PCR testing. 85.7% of patients who were asymptomatic for COVID-19 had no chest X-ray changes on admission vs 14.3% who had pneumonia on admission despite being asymptomatic, which supports the idea that COVID-19 patients could present with stroke, much earlier than respiratory involvement can be objectively demonstrated. 61.5% of patients who presented with a normal chest X-ray went on to develop Pneumonia during hospital stay, which strongly suggests that stroke in COVID-19 patients could be the consequence and the first feature of an inflammatory state triggered by SARS-CoV-2.

SARS-CoV-2 has also been strongly associated with increased risk of venous and arterial thrombosis [10]. The COVID-19 associated coagulopathy was well

reflected in our patients by raised D-Dimer levels in 58.3% and a modest increase in Prothrombin time in 95.8%. Raised inflammatory markers such as CRP, Procalcitonin and Ferritin, question the presence of inflammatory cytokines and their role in disrupting the blood brain barrier and resulting in neuro-inflammatory states that can precipitate cerebrovascular accidents, altered mental status, ataxia and seizures [11]. More than half of our patients presented with a raised procalcitonin on admission, while elevated levels of CRP and Ferritin was noted in 45.8% and 25% of patients respectively.

Our study was limited by the sample size of 24 patients, as it limited the diversity of clinical characteristics to be studied. In addition, due to logistical reasons including infection control policies and transfer of patients to other hospitals, complete stroke workup including transthoracic echo and carotid Doppler ultrasound could not be done in our facility; which could have added to the accuracy of number of thrombotic vs embolic sources of stroke.

6. Conclusion

Stroke is a well-studied clinical entity with various established risk factors and conventional clinical picture. However, during this pandemic increasing numbers of patients with COVID-19 infection are presenting with stroke and who either have no conventional risk factor or have apparently well controlled risk factors. It is imperative to consider the neurological impact of SARS-CoV-2 and its potential as a stroke risk factor, as stroke may be the presenting feature of COVID-19.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Experience of Management of Anorexia Nervosa Patients with Extremely Severe Malnutrition in a Transdisciplinary Clinical Nutrition-Eating Disorders Inpatient Unit

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Abstract

Background: The question of where to hospitalize extremely malnourished patients with anorexia nervosa (AN) is a real dilemma. On one hand, psychiatrists have to deal with severe medical complications that are not within their competences and that justify hospitalization in an internal medicine ward. On the other hand, medical doctors have to face psychic decompensations that would justify admission to a psychiatric ward. In this context, we share our experience of management of severely malnourished AN adult patients in a transdisciplinary specialized eating disorders (ED) unit, referral center for AN associated with somatic severity. **Method**: First, we described the modalities of care proposed to patients with AN hospitalized in the medical unit. Intensive medical care, both somatic and psychiatric, are provided thanks to a transdisciplinary therapeutic program, where objectives are to: medically stabilize the patient, initiate progressive refeeding and start supportive psychotherapy before being transferred to a psychiatric ED unit. Secondly, we conducted a retrospective descriptive study that included all adult patients with AN admitted for the first time to the unit, between November 1997 and January 2014, for severe malnutrition and/or complications of the ED. Objective was to specify patients' characteristics: demographic, nutritional status, history of ED, care pathway. **Results**: Among a cohort of 386 adult patients with AN (21 males and 365 females) admitted for the first time in the unit, mean age was 29.4 (±11.5) years, mean BMI was 12.7 (±2.2) kg/m^2. Be-

fore being supported in the unit, 78.2% of patients had already been hospitalized in other hospitals. Mean length of stay was 35.2 days. Patients were clinically serious and unstable because of life-threatening somatic complications due to a low BMI. During hospital stay, a temporary transfer to medical intensive care unit was necessary for 25.6% of patients. Average patient weight gain was 0.777 kg per week and 81.9% of patients benefited from enteral nutrition. **Conclusion**: This specialized transdisciplinary unit where physician nutritionists and psychiatrists coordinate medical care together, allow a better understanding and management of extreme malnutrition associated with AN. Thanks to their expertise, care teams are less critical and less rejecting towards patients. Thus, therapeutic alliance could be optimized.

Keywords

Anorexia Nervosa, Severe Malnutrition, Referral Center, Transdisciplinarity

1. Introduction

With a Standardized Mortality Ratio (SMR) estimated at 5.86 [1], anorexia nervosa (AN) is a serious psychiatric disease whose mortality rate is one of the highest of all psychiatric pathologies [2]. This mortality is especially high in tertiary care centers that treat the most severe forms of the disease (SMR at 10.6) [3]. Indeed, AN can cause severe undernutrition, which can lead to medical complications and expose the patient to life-threatening risks. Thus, more than half of the deaths (54%) of patients with AN are attributable to the medical complications of AN, including undernutrition [4]. Moreover, psychiatric comorbidities often accompany the undernutrition, which makes the patient's treatment more difficult to manage. Therefore, AN requires specific care. Most treatment programs provide medical and psychiatric components in the same milieu to optimize treatment to the extent possible.

But when a patient's nutritional status is too altered, (extremely severe undernutrition with BMI 8 kg/m^2 to 13 kg/m^2) careful weight restoration with refeeding must be conducted in an inpatient medical facility to limit the risk of refeeding syndrome (RS). Nutritional rehabilitation often corresponds to "nutritional resuscitation" in extreme forms of AN. In addition, somatic complications associated with psychiatric comorbidities are often worse and difficult to manage in a non-medical unit [5].

Our team has developed since 1997 a clinical nutrition unit specialized in the management of extremely severe undernutrition and its somatic complications resulting from different illnesses (peculiarly patients with HIV, chronic illnesses and eating-disorders (ED)) in adult patients. It was localized in Raymond Poincaré (RP) University-Hospital (Garches, 92380, France)[1]. It has been progressively oriented towards the exclusive care of patients with ED with life-threatening

[1]The clinical nutrition unit at Raymond Poincaré university hospital was transferred to Paul Brousse university hospital in September 2019.

medical complications. Since 2004, the clinical nutrition unit was only dedicated to the management of extremely severe undernutrition and its complications associated with ED.

Thanks to its expertise, the unit is now considered, in France, a regional and national "referral center" by the administrative authorities for the treatment of patients with AN whose clinical condition can be serious and complicated. The unit is a partner of both the regional ED professional network, "Réseau TCA Francilien", and the national ED professional network, the "French Federation Anorexia Bulimia" (FFAB), associating all ED professionals in a collaborative network.

Our unit is a 15-bed unit in a conventional inpatient hospital setting.

In order to prevent runaways and suicide attempts, (which is high risk in compulsory hospitalisations), the unit is equipped with secure equipment and controlled access. It is only possible to enter or leave the unit by using a specific code (password). In addition, videophones allow caregivers to open the unit's entrance briefly, as necessary. To further enforce the security, all windows are locked and lined with an anti-burglary glass, measures designed to protect the patients.

The medical team is composed of two physicians, an assistant physician, two psychiatrists and two internal medicine residents who are interested in nutritional care. The paramedical team consists of a pool of 10 nurses, 8 nursing assistants, a nursing supervisor, a clinical psychologist, a social worker, a dietician and a physiotherapist.

Ambulatory care is also provided in the department to assess patients before their hospitalization in the unit and to follow them after discharge. It is represented by two weekly outpatient consultations and by day-activities. The mission of the outpatient clinic is to provide comprehensive clinical assessments: complete nutritional and psychiatric assessment as well as screening for complications related to under-nutrition. It is a transdisciplinary outpatient clinic; a nurse, a dietician, a physician nutritionist, a psychiatrist and/or a psychologist, evaluate patients successively (or jointly).

Our clinical nutritional rehabilitation team has developed expertise in treating extreme malnutrition due to severe AN. In order to deliver tailored care for the most severe cases of AN, we developed a transdisciplinary medical and psychiatric unit including both medical and psychiatric care in RP Hospital.

The goal of this paper is to describe this transdisciplinary program of management of emaciated patients with severe forms of AN and the characteristics of patients hospitalized in the unit. We will explain the modalities of somatic and psychiatric care proposed, and we will describe patient characteristics and patient care pathways. We will then discuss the potential benefits that the development of such a unit could bring.

2. Materials and Methods

2.1. Study Design and Aims

The primary objective was to describe the modalities of somatic and psychiatric

care proposed to patients with AN hospitalized in the clinical nutrition unit.

The secondary objective was to specify characteristics of patients with AN hospitalized in the clinical nutrition unit: demographic, nutritional status, history of ED, care pathway. In order to do so, we conducted a monocentric retrospective observational descriptive study in the cohort of adult AN patients admitted to the clinical nutrition unit in RP hospital for severe malnutrition and/or complications of the ED.

2.2. Description of Inpatient Treatment and Management

2.2.1. Objectives of Treatment in a Full-Time Hospitalization

Inpatient treatment has the following objectives:

- Begin a careful and gradual refeeding to stabilize critically ill patients suffering from severe malnutrition before they are transferred to a psychiatric inpatient unit specialized in ED. Psychiatric units are not usually sufficiently equipped and do not have the medical competence to handle the first stage of intensive care in case of severe malnutrition [6] [7].
- Diagnose and treat any medical complications.
- Initiate, continue or resume psychiatric care. The objectives of psychiatric intervention at this stage of undernutrition are limited to: detecting and preventing any suicidal behaviour, taking security measures to protect the patient if necessary, providing supportive therapy and creating specific a short-term and long-term treatment plan.
- Decrease invasive binging and purging behaviors, (self-induced vomiting, laxative or diuretic abuse), potomania, and problematic exercising, as necessary.
- Effort to preserve and improve the socio-professional integration of the patient (if deficient) in anticipation of his discharge from the hospital.

To achieve these goals, medical care should be multifocal and therefore transdisciplinary including meetings to coordinate planning. Two different transdisciplinary staff meetings are organized regularly to optimize and coordinate patient care.

In addition, the therapeutic alliance between the patient and the healthcare team is essential to the efficacy of the treatment program. Ideally, (except in cases of emergency hospitalization), the conditions of hospitalization are discussed in advance with the patient and his family during a pre-admission consultation.

2.2.2. The Individualized Therapeutic Program

The therapeutic program is adapted to each patient specifically. A written care contract is agreed between the patient and his caregivers. It sets out weighted objectives and the steps needed to combat anorexic cognitions. The conditions of hospitalization are also explained and detailed. Discharge planning for the continuation of medical care (specifying the medical team and treatment facility) is determined progressively based on discussions with the patient and his family as clinical improvement of the patient progresses.

2.2.3. Enteral Nutrition

When a patient's BMI is below 13 kg/m^2, artificial nutrition support is usually indicated to initiate the refeeding of the patient [7], taking into consideration his clinical condition (presence of edema, physical exhaustion), his calorie intake and his blood test results[2] [8] [9]. The existence of medical complications weighs in favor of instituting nutritional support therapy[2]. When a patient's BMI is less than 12 kg/m^2, artificial nutrition is systematically proposed from the start [6] [8] [9].

Assuming the patient has an accessible and intact digestive tract (which is true in most cases) [10], the choice of nutritional support is typically enteral nutrition (EN) administered via a small-caliber nasogastric tube as recommended [6] [11]. Parenteral nutrition is not used in AN [6] [12] [13] [14]. Vomiting is not a contraindication to EN.

The good tolerance of EN [15], its effectiveness on both weight gain (a weight gain between 500 g and 1 kg per week is recommended [6]) and on the reduction of the duration of hospitalizations, have been demonstrated [16] in malnourished patients with AN.

EN is prescribed in the following manner:

- A standard polymeric product, isocaloric (providing 1 kcal/ml) [6] [17], normoprotidic [17], without fiber[2] is most often prescribed
- As excessive protein intake is hazardous in cases of impaired renal function [17] or particularly in very low weight patients, a paediatric product less rich in protein is preferred[2] in that cases.

To improve its performance and clinical and metabolic tolerance, EN is administered in a continuous flow over 24 hours [11] [17] using a flow control pump. When undernutrition is extremely severe (BMI < 12 kg/m^2), refeeding is exclusively enteral in the first days[2]. An oral diet is gradually introduced later[2] (see dietary management).

Calorie intake is started at 10 kcal/kg body weight/24 hours during the first 48 hours as recommended with severely malnourished patients [17]. Then it is increased gradually [17] in increments of 250 kcal, according to the patient's clinical and biological tolerance, to reach 45 kcal/kg body weight/24 hours.

2.2.4. Hydration, Vitamins and Trace Elements

During the first 48 hours of hospitalization, intravenous supplementation with vitamins, trace elements and phosphorus is carried out to correct potential micronutrient deficiencies and to prevent RS as recommended [6] [17] [18]. Intravenous rehydration with a 5% glucose polyionic solution is also administered, limited to 30 ml/kg body weight/24h. Patients are put on a low sodium diet (sodium intake < 1 mmol/kg body weight/24h) to prevent water inflation. Daily intake of phosphorus, vitamins and trace elements is continued orally [6] [17].

Additional intravenous contributions of potassium, magnesium and phosphorus are added in case of hypokalemia, hypomagnesemia or hypophosphate-

[2]Specific practice in the unit based on expert opinions (and not on standard feeding protocols).

mia [6] [17].

2.2.5. Oral nutrition

Dietary management is an integral part of overall care and it becomes more and more important with the progression of the patient's hospitalization, in parallel with the decrease in EN [6] [17]. The reintroduction of oral feeding is done gradually, once refeeding has begun and in the absence of critical metabolic abnormalities, at a rate adapted to the physiological and psychological capacities of the patients. The reintroduction of food must be progressive, as under-nutrition is severe [6] [7].

Protein foods are re-introduced last (after vegetables and carbohydrates)[2], in order to limit protein intake at a level under 2.5 g/kg of body weight per day. Oral feeding is carried out with 3 meals per day and, if necessary, a snack at 4 pm. The meal duration must not exceed 30 minutes for lunch and 45 minutes for dinner[2].

A food-monitoring sheet is displayed in the patient's room which notes the current oral intakes of the patient. Once established, the composition of the meal can only be changed after the dietician has interviewed the patient. As oral nutrition and weight gain are acquired, enteral caloric intakes are progressively reduced [17]. It is recommended to interrupt EN if the oral intake is satisfactory when the BMI is around 14 kg/m^2 [17].

2.2.6. Prevention of Refeeding Syndrome

The severe and chronic undernutrition of the patient with AN (BMI < 16 kg/m^2) exposes the patient to an increased risk of RS at the initial phase of refeeding [6] [19]. The metabolism of the patient, which was idling in a state of adaptation to prolonged fasting, faces a new situation: the reintroduction of nutrients and its resulting increase in insulin levels [20]. This metabolic change puts the patient at risk, especially if the increased calorie intake is not introduced gradually, with movement of water and electrolytes from the extracellular sector to the intracellular sector. RS can manifest with ionic disorders, (mainly hypophosphatemia, hypokalemia and/or hypomagnesemia), fluid retention and one or more organ dysfunction(s) (acute heart failure, renal failure, respiratory failure, liver failure, convulsion or even coma) [17] [21].

To prevent RS, various measures are implemented:

- Refeeding is started with a minimum calorie intake, then increased very gradually, following the rule "start slow, advance slow." [6] [17] [20]
- Adjustment of calorie intake is individualized to the patient's metabolic tolerance and weight gain. Ideally, the weight gain should be 0.5 to 1 kg/week [6] [17] [20]
- Supplementation with multivitamins, trace elements, potassium, phosphorus, and magnesium is started empirically from the first day of admission, and then adapted, based on the biological results [6] [17]
- Comprehensive clinical monitoring with special attention to heart rate, edema and hydration status [6] [17]

- Regular biological monitoring (initially daily during the first week of hospitalization) of blood glucose, creatinine, liver enzymes, plasma electrolytes, and phosphorus [6] [17] [20]. Later, blood tests are repeated once a week if there is no acute abnormality [6] [17].

2.2.7. Psychotropic Treatment

There is no specific psychotropic treatment for AN [6] [22] and those medications can have severe side effects in case of malnutrition. This is the reason why psychotropic medications are not systematically ordered in the unit. However, as recommended in all international guidelines [22], antidepressant medications are occasionally used when the patient still presents anxious depressive symptoms leading to an anxious or depressive disorder diagnosis despite a significant improvement in his nutritional status [23]. Antidepressant prescription is ordered by psychiatrists only with strict monitoring of potential adverse effects (in particular cardiac). It only concerns a small subgroup of patients whose nutritional status allows. When the patient's anxiety symptoms are so severe that it is a barrier to his refeeding process, a small dose of anxiolytics can also be prescribed.

2.2.8. Prevention of Decubitus Ulcers and Deep Vein Thrombosis

Strict bed rest is ordered in the beginning of hospitalization. It can be extended for some patients. Daily nursing care provided by nurses and nursing aids, and the use of air mattresses are the main measures to prevent bedsores in the unit. In addition, a prophylactic dose of anticoagulant treatment is ordered to prevent deep vein thrombosis.

2.2.9. Blood Analysis and Imaging

Some analyses are carried out during the early phase of the hospital stay, as recommended [6] [17]:

- Blood analysis (complete blood count (CBC), platelets count, electrolytes, urea, creatinine, calcium, phosphorus, magnesium, albumin, transthyretin, glycemia, liver enzymes, prothrombin time (PT), partial thromboplastin time (PTT), C-reactive protein (CRP), Thyroid Function Tests, folate, vitamin B12, vitamins A, D and E, zinc, copper, selenium)
- Electrocardiogram (ECG)

A bone densitometry is done to assess the patient's bone mineralization status and to detect potential osteoporosis. It may be the first time a patient has had a bone densitometry in his medical history. If the patient had already a bone densitometry done in the past, a waiting period of two years is needed before repeating it [6].

An echocardiogram is also provided in the presence of clinical signs of cardiac insufficiency and/or ECG abnormality.

2.2.10. Clinical and Bio-Clinical Monitoring

An internal medicine doctor and a psychiatrist perform daily ward rounds together. All the patients present in the ward are seen every day by the team of

doctors who provide physical examinations, discussions about hospitalization conditions, adjustment and revaluation of treatment, management of acute medical issues. Thus, each medical complication is managed adequately.

2.2.11. Psychiatrist's Role

All hospitalized patients are assessed by psychiatrists through structured interviews with particular attention to the search for psychiatric comorbidities. Psychiatrists manage acute psychiatric symptoms. They are responsible for prescription of psychotropic medications when needed, according to the patient's biological and clinical tolerance. In cases of compulsory hospitalization, they write medical certificates in collaboration with the medical doctor.

In cooperation with psychologists, psychiatrists provide supportive psychotherapy. Structured therapy is difficult and may be impossible in case of extremely severe malnutrition. In fact, some psychiatric symptoms can be caused by malnutrition. Moreover, in the early phase of hospitalization, cognitive functions are altered by undernutrition itself [20].

2.2.12. Psychologist's Role

The psychologist is responsible for individual psychotherapy support for each patient at least once a week. The frequency of these interviews is adjusted taking into account both the patient's preferences and the medical and psychiatric teams' evaluation. The psychologist also coordinates group activities or occupational therapy (3 times per week) to enable the patient to build alliances with the team and develop social relationships based on mediational activities. Different themes are explored through these activities. The different workshops include: group therapy focused on life and treatment in the unit, a newspaper workshop, cultural mediation, creative arts, and writing. Patients are invited to participate as soon as their physical conditions allow it.

2.2.13. Discharge from the Unit and Continuation of Care

When a patient leaves the zone of critical danger, and his clinical condition is stable, he can be discharged. The refeeding process should achieve a minimum BMI of 13 kg/m^2. From then on, usually patients are transferred to an ED psychiatric unit to continue the refeeding process and initiate ED specialized therapies. This transfer is organized when the patient agrees. But some patients are unwilling to accept the transfer. When this occurs, there are two possibilities: if their clinical state is still critical, a compulsory treatment is implemented in the ED psychiatric unit; if not, they are discharged to ambulatory treatment. When the transfer takes place, it is preceded by a pre-admission consultation in the designated specialized ED psychiatric unit. Follow-up care can also be provided in a conventional psychiatric unit.

2.3. Patients

2.3.1. Inclusion Criteria

We selected all patients hospitalized for the first time in the CNU in RP Hospital

between November 1997 and January 2014, aged 15 years or older, diagnosed with AN according to the DSM IV criteria [24]. The patient selection was provided by the hospital's department of statistics and medical information.

2.3.2. Exclusion Criteria

We excluded from the study any patients who did not allow the use of their data for the study.

2.3.3. Parameters Studied

For each patient, we performed a retrospective chart review and we recorded demographic and anamnesic data. Subtype of AN (binge-eating/purging subtype, "AN-BP", defined by the presence of binge-eating (eating within any 2-hour period an amount of food that is larger than most people would eat with a sense of lack of control over eating) and/or purging behaviour (self induced vomiting, misuse of laxatives, diuretics) [24] or restricting subtype, "AN-R", defined by the absence of binge-eating or purging behaviour [24]), duration of disease, purging behaviours, history of hospitalization for AN were detailed. Anthropometric data on admission and on discharge were noted as were patient psychiatric comorbidities, referral, length of stay and any intercurrent events which occurred during hospital stay.

2.4. Procedures and Ethical Approval

This study was conducted in accordance with the relevant French guidelines and regulations. It is part of a mortality study for which protocol was approved by the French data protection authority (CNIL, *Commission Nationale de l'Informatique et des Libertés*) and by two independent review boards (CCTIRS, *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* and CPP, *Comité de Protection des Personnes*). An information letter was sent to all patients selected for the study. Patient non-opposition was a prerequisite for the use of their data. Written informed consent for publication was obtained.

2.5. Statistical Analysis

Analyses were performed with R software (version 3.5.3. 2019-03-11, R Foundation for Statistical Computing Platform: x86_64-w64-mingw32/x64 (64-bit)). Univariate statistics were used to describe the sample. Data were expressed as frequencies and percentages for nominal variables, and as means ± standard deviations (SDs) for continuous variables.

3. Results

3.1. Patient Characteristics

Initially, 395 patients were selected but 9 of these were excluded because they declined use of their data in the study. Finally, we included a total number of 386 patients: 365 (94.6%) were female and 21 (5.4%) were male. Mean age at admis-

sion was 29.4 (±11.5) years old. Duration of AN at admission was 9.9 (±9.3) years. BMI at admission was 12.7 (±2.2) kg/m^2.

To achieve this weight gain, EN was widely prescribed in our cohort: 316 (81.9%) patients benefited from EN during their hospital stay. We observed that more than one-third of patients were still on EN on discharge: 137 (35.5%) patients were still receiving EN when they left the unit. Hence, EN was ongoing in their transfer unit to continue the refeeding process.

Patient characteristics are presented in Table 1.

Table 1. Patient characteristics (N = 386).

Characteristics	Mean ± SD or N (Percentage)
Female/Male	365 (94.6%)/21 (5.4%)
Age at admission (years)	29.4 (±11.5)
Subtype of anorexia nervosa:	
Restricting	180 (46.6%)
Binge-eating/purging	186 (48.2%)
Atypical AN	20 (5.2%)
Age at AN onset (years)	19 (±7.6)
Duration of AN at admission (years)	9.9 (±9.3)
History of hospitalization for AN in other hospitals (before admission in the unit)	302 (78.2%)
Number of hospitalizations for AN (before admission in the unit)	2.9 (±3.4)
Patient's regular behavior:	
Self induced vomiting	162 (42%)
Laxative misuse	81 (21%)
Potomania	54 (14%)
Diuretic use	15 (3.9%)
Problematic exercice	175 (45.3%)
BMI (kg/m^2):	
Admission	12.7 (±2.2)
Discharge	14.2 (±1.9)
Weight gain during hospitalization (kg)	3.8 (±4)
Psychiatric comorbidities:	
Personality disorders	84 (21.8%)
Obsessive-compulsive disorders	32 (8.3%)
Mood disorders and/or Anxiety disorders	181 (46.9%)
History of suicide attempt	81 (21%)
Self-mutilations (nonsuicidal self-injury disorder)	28 (7.3%)
Attention Deficit Hyperactivity Disorder	5 (1.3%)
Kleptomania	3 (0.8%)
Addictions:	
Alcohol use disorder	34 (8.8%)
Substance use disorder	24 (6.2%)
Tobacco use disorder	127 (33%)

3.2. Patient's Referral to the Unit

Among the patient cohort, the most frequent reason for admission was extremely severe undernutrition. It concerned 295 (76.4%) patients. Fifty-four (14%) patients were hospitalized for other reasons such as the treatment of one or more medical complications related to undernutrition or to the process of refeeding itself initiated outpatient or inpatient in other hospitals. Short admissions were also organized for nutritional evaluation and development of a treatment regime in 19 (4.9%) patients. Finally, 18 (4.7%) patients were admitted in order to wean purging behaviours (self-induced vomiting, laxative or diuretic abuse).

The protocol for the treatment of patients in the unit was individualised following an initial consultation or evaluation in psychiatric or general medicine day hospital. In case of emergency, the patient could be also admitted after a transfer from an inpatient unit in another hospital (e.g., an emergency room, medical ward, medical intensive care unit (MICU), or psychiatric ward), (refer to Table 2).

3.3. Length of Stay, Number of Admission

Our unit has 180 to 200 admissions per year with an average length of stay of 35.2 (±30.2) days. Patients can be hospitalized multiple times in the unit if necessary. Among the cohort, 127 (32.9%) patients were re-hospitalized one or more times in the unit after their first admission because of a somatic complication and/or a relapse of the disease resulting in a life-threatening clinical condition, within 1.7 (±1.5) years, over the study period from November 1997 to January 2014.

3.4. Medical Management Difficulties

Because of the extreme severity of the patients' medical conditions and despite

Table 2. Distribution of medical units that referred the patients to the unit (n = 366).

Medical unit that referred the patients to the unit	N (Percentage)
Psychiatric inpatient unit	54 (14.8%)
Emergency department	25 (6.8%)
Medical Intensive Care Unit	65 (17.8%)
Medicine outpatient clinic	100 (27.3%)
Psychiatric outpatient clinic	59 (16.1%)
Medical ward	51 (13.9%)
Student medical and psychiatric clinic	2 (0.5%)
Adolescent care inpatient unit	3 (0.8%)
Surgical ward	1 (0.3%)
Obstetrics and gynecology inpatient unit	2 (0.5%)
General pediatrics inpatient unit	4 (1.1%)

all the precautions taken during the refeeding process, some acute medical complications could appeared. It was rarely a refeeding syndrome (23 cases in our cohort-5.9% of patients); most often, these complications corresponded to: hemodynamic instability, electrolyte imbalance, anemia, severe neutropenia, acute organ dysfunction (cardiac, hepatic, renal) or sepsis linked to the relative immunosuppression induced by the malnutrition. Consultations to other sub-specialties such as infectious diseases or hepatology could also be required to optimize the management of patients at times.

All these situations were managed individually. In cases of critical or unstable clinical parameters or vital organ dysfunction, a transfer to the MICU was organized. Among our cohort, 99 (25.6%) patients were temporarily transferred to the MICU during their hospitalization in the unit. Reasons for these MICU transfers are presented in Table 3.

3.5. Psychiatric Care Difficulties

Main difficulties encountered in psychiatric care were: the presence of psychiatric comorbidities (refer to Table 1), cases of runaways (9 cases in our cohort—2.3% of patients) and case of discharges against medical advice before the end of

Table 3. Reasons for MICU transfer during the hospitalization in the unit.

Reason for medical intensive care unit (MICU) transfer during hospitalization in the unit	Number of patients	Percentage of the total number of MICU transfers (N = 99)
Hypokalemia complicated by ECG changes	21	21.2%
Hypophosphatemia complicated by ECG changes	11	11.1%
Severe hyponatremia[1]	9	9.1%
Severe hypertransaminasemia[2] and hepatic failure	20	20.2%
Acute cardiac failure	6	6.1%
Hemodynamic instability and/or cardiac arrhythmias	24	24.2%
Hypothermia	5	5%
Acute renal failure	10	10.1%
Suicide attempt	8	8.2%
Acute pancreatitis	1	1%
Severe sepsis[3]	14	14.1%
Anasarca	3	3%
Neurological disorders	5	5%
Severe symptomatic hypoglycemia[4]	6	6.1%
Gastric distension	1	1%
Parenteral nutrition use	1	1%

[1]: Hyponatremia < 120 mmol/l; [2]: Elevated Liver Function Tests with aspartate transaminase and alanine transaminase ≥ 10 times the normal upper limit; [3]: Sepsis associated with organ dysfunction, hypoperfusion or hypotension; [4]: Hypoglycemia < 2.8 mmol/L associated with neurological symptoms.

the care protocol (46 cases among our cohort – 11.9% of patients without immediate life-threatening conditions). However, in cases of vital risk, (when the patient's condition is compromised and the continuation of refeeding is urgently required), if the patient does not agree to the continuation of care, a legal procedure for compulsory treatment under French Law can be implemented in the unit. This procedure is developed in collaboration with the regional reference psychiatric center and implemented in our medical unit until the clinical state of the patient allows other modalities of treatment. In our cohort, 24 (6.2%) patients were affected by this procedure.

3.6. Discharge from the Unit

The different facilities receiving the patients after hospitalization in the unit are presented in Table 4. In our cohort, 44.1% of patients benefited from a transfer to a psychiatric ward (general psychiatry, psychiatric unit specialized in ED, psychiatric rehabilitation center) and 43.8% were discharged at home after hospitalization in the unit (refer to Table 4). Among the patients discharged at home, 11.9% were discharged against medical advice and 31.9% were allowed to leave the unit under medical team permission.

4. Discussion

The question of where to hospitalize extremely malnourished patients with AN is a real concern raised in the literature by psychiatric teams specialized in the

Table 4. Distribution of facilities receiving patients after discharge from the unit (N = 386).

Facility receiving the patient after discharge from the unit	N (Percentage)
Home	169 (43.8%)
General psychiatry	45 (11.7%)
Psychiatric unit specialized in eating disorders	116 (30.1%)
Medicine rehabilitation center	6 (1.5%)
Nutrition rehabilitation center	8 (2.1%)
Psychiatry Day Hospital	14 (3.6%)
Endocrinology department	1 (0.3%)
Surgical ward	4 (1%)
Psychiatric rehabilitation center	9 (2.3%)
Internal medicine ward	3 (0.8%)
Clinical nutrition unit	1 (0.3%)
Home hospitalization	1 (0.3%)
Obstetrics and gynecology department	2 (0.5%)
Medical Intensive Care Unit	1 (0.3%)
Death during the hospital stay	6 (1.5%)

management of AN [25] [26]. It may seem like a dilemma. On one hand, in case of extreme malnutrition related to AN, psychiatrists have to deal with severe medical complications that are not within their competences and that justify hospitalization in an internal medicine ward. On the other hand, medical doctors have to face the resistance to treatment inherent to patients with AN (denial, treatment refusal, ambivalence about treatment) and psychic decompensations that would justify admission to a psychiatric ward [25]. This problem is mentioned in the MARSIPAN report which specifies that specialist-ED-units are not suitable for treating severe medical complications [26]. Thus, a survey in specialist-ED-units published by the MARSIPAN working group showed that services could not offer intravenous infusion, parenteral nutrition and treatment of serious medical complications in these units. Patients with electrolyte or renal abnormalities or comorbidity increasing the risk of refeeding syndrome should not be managed in a specialist-ED-unit. MARSIPAN guidelines recommend to transfer these patients to a medical ward. Then there are the issues of liaison and transfer between the two settings (specialist-ED-unit and medical ward) [26].

Our unit responds to this problem by providing both somatic and psychiatric care, in the same place, to make the management of severely malnourished patients with AN more safe and effective.

The development of a team specialized in the management of severe malnutrition and the regular admission of patients with AN in the unit has allowed us to develop expertise in the most extreme clinical situations. As explained by E. S. Chu [27], the management of patients with complex illnesses, is better when it is provided by a medical team with specific expertise. In this context, transdisciplinary management involving psychiatrists and medical doctors appears essential. Indeed, the goal of having a transdisciplinary team is to respect the patient's individuality by proposing both a global and a personalized approach. The teamwork of the different professionals who exchange ideas and mutually enrich each other makes it possible to offer optimal care for the patient.

The other specific benefits of transdisciplinarity are the possibility of: initiating early psychiatric follow-up, ensuring continuity of care by preparing for subsequent care in specialized ED psychiatric unit, initiating compulsory treatment if necessary. Thanks to the centralization of treatment for difficult medical situations, the unit has become an important referral center for effective treatment of serious ED.

The development of the therapeutic alliance is favored by the involvement of the close entourage of patients in the care program. The involvement of the families is an important factor in patient adherence to care [28].

To the best of our knowledge, we did not identify either in France or elsewhere in Europe, a similar unit providing simultaneously medical and psychiatric transdisciplinary combined care to patients with severe forms of AN: with psychiatrists and internal medicine doctors working full time in the same unit with daily cooperation and interactions. However, we did find an acute medical unit in Denver accepting patients with ED and severe medical complications

[27]. This unit does not have an onsite psychiatrist but psychologists can support the patients during their hospitalization. In Munich, there is also a psychiatric intensive care unit accepting severely malnourished patients with AN for refeeding since 2000 [29]. There is no internal medicine doctor working full time in this unit but if necessary, opinions for the somatic management of patients are requested by psychiatrists from internal medicine doctors working in the internal medicine department of the hospital.

Providing in parallel, in the same venue, both medical and psychiatric care in a transdisciplinary way to patients with severe forms of AN appears essential for patients and care givers as we discussed previously. That is why our transdisciplinary model of treatment could be adapted in other treatment programs (medical or psychiatric) for severe AN. Hence, medical units who are receiving malnourished patients with AN could integrate a psychiatrist specialized in ED, into their teams, to complement medical care with psychiatric support. And, psychiatric units specialized in ED could integrate a physician-nutritionist, into their teams, in order to manage EN prescription, refeeding process and medical complication in case of extreme malnutrition.

This transdisciplinary program which provide both somatic and psychiatric treatment could allow a more complete and global care of patients suffering from AN. It could also facilitate management of patients with extreme malnutrition and/or medical complications. Indeed, such patients cannot be admitted directly to psychiatric Specialist-Eating-Disorders-Unit due to the severity of their somatic condition. With a transdisciplinary model of treatment, Specialist-Eating-Disorders-Unit could be able to admit such patients.

We formulate the hypothesis that a transdisciplinary model of treatment could optimize and improve the quality and effectiveness of care for patients with AN. However, the positive impact of this model needs and remains to be proven, particularly in terms of clinical or public health benefits. Does this model of care could participate to reduce chronicization of disease, frequency of relapse, number of admission, length of stay or patient mortality? It would be interesting to study all these parameters.

We share the opinion of E.S.Chu [27] that this rare, medically unstable and complex population of patients with severe malnutrition secondary to AN requires a specific medical management by a highly specialized multidisciplinary team within a referral center. The team also has a mission, through clinical research perspectives, to provide a better understanding of the somatic complications associated with extreme malnutrition and thus participate in the elaboration of protocols and management guidelines [6] [30].

5. Conclusion

The transdisciplinary model of management and treatment of adult patients suffering from AN in the clinical nutrition-ED-unit in Raymond Poincaré-University Hospital could, if it were available more widely, benefit the most distressed pa-

tients and potentially decrease complications and mortality related to severe AN and promote patient care compliance. Thanks to their expertise, specialized care teams are very competent, less critical and less rejecting towards patients [31].

Declarations

Ethical Approval and Consent to Participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent was obtained from all individual participants included in the study.

Consent for Publication

Written informed consent for publication was obtained (please refer to paragraph: II.3. Procedures and ethical approval).

Availability of Data and Materials

The datasets generated and analysed during the current study are not publicly available due to other works being under progress but are available from the corresponding author on reasonable request.

Authors' Contributions

MG collected and analysed the patients' data and wrote the initial manuscript. JCM, NG and MH analysed the patients' data and contributed in writing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

The authors declare that they have no competing interests.

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List of Abbreviations

AN = anorexia nervosa
AN-R = anorexia nervosa restricting subtype
AN-BP = anorexia nervosa binge-eating/purging subtype
BMI = body mass index
CBC = complete blood count
CRP = C-reactive protein
ECG= electrocardiogram
ED = eating disorders
EN = enteral nutrition
MARSIPAN = management of really sick patients with anorexia nervosa
MICU = medical intensive care unit
PT = prothrombin time
PTT = partial thromboplastin time
RP = Raymond Poincaré
RS = refeeding syndrome
SMR = standardized mortality ratio

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Application of the Modality of Multiple Disciplinary Team for a Perioperative Patient with Suspected Novel Coronavirus Pneumonia and Cervical Spine Fracture in Nursing

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Abstract

With the explosive spread of novel coronavirus pneumonia, a major public major public health emergency has been declared around the world. Our country has come to a crucial stage of "external defense input, internal defense rebound" and strict quarantine measures are taken in all ports of entry throughout the country. Operations on patients with cervical spine during the quarantine, which not only increases the risk of surgical treatment, but also increases the difficulty of perioperative nursing. The objective is to explore the result of application of the modality of multiple disciplinary team for a perioperative patient with suspected novel coronavirus pneumonia and cervical spine fracture in nursing. The patient's condition and nursing measures are studied and discussed from various specialist angle through the multidisciplinary team established by the isolation ward, orthopedics department, emergency department, anesthesiology department, operating room, rehabilitation department, psychology department and so on, and the overall and personalized surgical and nursing planning is formed through interdisciplinary advice. The nursing experience is summarized in this paper.

Keywords

Multiple Disciplinary Team, Suspected Novel Coronavirus Pneumonia, Cervical Spine Fracture, Perioperative Period, Nursing

1. Background

The pneumonia of unknown cause has aroused extensive attention from our society because it progressed quickly and people were generally susceptible. It was

later identified by expert group of the National Health Commission as novel coronavirus pneumonia (hereinafter referred to as COVID-19) infection [1]. Droplet transmission and close contact transmission are the main routes of transmission and people are generally susceptible. The main symptoms of novel coronavirus pneumonia are fever, dry cough and fatigue and a few patients have nasal congestion, runny nose, sore throat diarrhea and other symptoms [2]. Although the prevention and control situation of COVID-19 has gradually improved in our country, the international situation is still breaking out and the importation situation is still grim. Special attention should be paid to preventing and controlling overseas input. One patients with COVID-19 and cervical spine fracture from abroad was admitted to our department. The patient has passed medical observation for further rehabilitation through close isolation and monitoring, timely surgical plan and proper nursing measures.

Multiple disciplinary team (hereinafter referred to as MDT) originated in the 1990s and was first proposed by the medical expert group in the United States. It refers to the clinical diagnosis and treatment mode of personalized diagnosis and treatment scheme for a certain system or organ disease through regular, fixed time and address specific meetings, which is generally composed of experts from two or more related disciplines. The purpose of this study is to provide patients with the most effective, minimal adverse reactions and the best quality of life on the basis of multidisciplinary demonstration. MDT reasonably and effectively utilizes and combines medical resources, which not only maximizes the advantages of medical personnel in various disciplines and greatly improves the therapeutic effect, but also improves the quality of medical service, patient satisfaction, the treatment efficiency and success rate of patients, and ensures the safety of patients [3].

2. Clinical Data

The 31-year-old male patient with incomplete paraplegia caused by a traffic accident started from Tanzania (epidemic area) on July 25, 2020 by the first-aid charter plane organized by International SOS organization, and arrived in Guangzhou through several countries. After arriving in Guangzhou, the negative pressure ambulance and medical staff of our hospital took him back to the isolation ward according to the requirements of secondary barriers.

The patient had repeated low fever on July 3, and the fever subsided on July 10. The nucleic acid results of COVID-19 detected in the local hospital of Tanzania are shown in the **Table 1** below.

The patient developed numbness of limbs and limited movement after a traffic

Table 1. The nucleic acid results of COVID-19 detected in the local hospital of Tanzania.

Date	3 July	10 July	16 July	20 July
Nucleic acid test results	positive	negative	negative	negative

accident one month ago, whose both lower extremities are much more severe and his left side was better than his right side. His hands and wrists were weak and could barely move. His lower limbs could not move, stand or walk. He was sent to the local hospital in Tanzania for treatment after the injury, but things didn't get better after a period of time treatment. Then he was admitted to our department for further diagnosis and treatment. He had no unconsciousness disorder, no coma, good spirit, body weight loss about 5 kg, uncontrolled defecation, indwelling catheter and good sleep after the injury. The nucleic acid and antibody results of COVID-19 were detected once he had been admitted to our hospital and both results were negative and all examinations were perfected. The results of CT and MR showed "C6 vertebral fracture, C5-7 vertebral arch fracture, C6 level spinal cord edema". Lower spinous process and vertebral column existed obvious tenderness by physical examination. The shallow sensation (warm pain sensation) below C4 level was weakened, while the deep sensation existed. The muscle atrophy of both upper limbs was evident, but the muscle tone was normal. The muscle strength of elbow flexion and extension of both upper limbs was grade 5, that of wrist extension and wrist extension was grade 3, that of finger flexion and abduction was grade 0. The muscle atrophy of both lower limbs was slight, and the muscle tone was subdued. The muscle strength of left lower limb dorsum extensor was grade 4 and that of other two lower limbs was grade 0. The primary diagnosis was "spinal cord injury (C6 level), spinal fracture (C4-6), acute incomplete quadriplegia". On July 26, 2020, the patient underwent "anterior C6 vertebral subtotal resection+ anterior spinal canal decompression+ titanium mesh bone graft reconstruction+ plate and screw internal fixation" under general anesthesia. After the operation, the patients were treated with neck fixation, inhibition of postoperative inflammation and edema, inhibition of gastric acid, nutritional nerve, rehabilitation physiotherapy and functional training. The patient was in stable condition and was transferred to rehabilitation department for further rehabilitation treatment on August 8, 2020.

3. Multidisciplinary Cooperation Mode

3.1. Build a Team

It was a suspected COVID-19 patient who returned to China from the epidemic area and had cervical spine fracture that required surgical treatment and postoperative rehabilitation, which involved many disciplines, such as emergency transportation, emergency, orthopedics, anesthesia, surgery, rehabilitation exercise. Our hospital is a large 3a general hospital which is also a provincial designated hospital to treat patients with COVID-19. We immediately set up a multi-disciplinary cooperation team, including isolation ward, orthopedics, emergency department, anesthesiology department, operating room, rehabilitation department, psychology department and other related medical personnel after receiving the task. The responsibilities of team members are shown in the **Table 2** [4].

Table 2. The responsibilities of team members.

member	duty
Emergency Department	Transfer the patient and make handover with the staff of isolation ward
Isolation Ward	Admission education, preoperative preparation, observation and nursing of postoperative complications, postoperative guidance of early rehabilitation exercise, timely inform orthopedic doctors on duty when abnormal conditions are found
Anesthesiology Department	Complete preoperative anesthesia visit, evaluate operation risk, formulate specific anesthesia scheme, communicate with the patient's family
Operation Room	Prepare the negative pressure operating room, check and adjust the intraoperative materials one day in advance, evaluate the operation position together with the anesthesiologists and orthopedics personnel, and place the patient's position carefully
Orthopaedics Department	Preoperative discussion to determine the surgical plan and implementation of surgery, daily medical rounds, guidance of isolation ward staff to do a good job in early rehabilitation training
Rehabilitation Department	According to the postoperative situation, the individualized rehabilitation program was formulated, and early physical exercise and rehabilitation therapy were performed
Psychology Department	According to the demands of patients, targeted psychological counseling, convey greetings from relatives and friends, and enhance the rehabilitation confidence of patients

3.2. Implementation Plan

3.2.1. Standardized Personnel Training

After receiving the task of treating the wounded, our medical workers in isolation ward immediately entered the preparation state and improved the training contents, including learning of inpatient environment, use of protective equipment, accountable and overall nursing care plan, related knowledge of the COVID-19, treatment plan, nursing measures and so on [4]. We participate in a week of theoretical and operational training in the orthopedics department, and all the staff were proficient in the key contents such as axis turning method, neck brace fixation, breathing and limb function exercise, and postoperative evaluation and observation. At the same time, medical workers confirmed that the articles in the isolation ward were in emergency and complete state, and determined the inspection route, transportation and operation route, and the main contents of succession.

3.2.2. Preoperative Case Discussion

On the day of admission, the orthopedic doctors worked out the operation method and date based on the results of various examinations. The anesthesiologist completed the preoperative visit and evaluated that the general and endotracheal intubation conditions were good. In the morning of the operation day, after the operation team checked the patients in bed, the operation, anesthesia and nursing teams conducted preoperative discussion. The surgeons and anesthesiolo-

gists talked with the family members of the patient after the unified plan. Family members sign the relevant informed consent. The medical staff in the isolation ward completed preoperative fasting and water deprivation, skin preparation, blood matching, oral care, skin care, urethral care, prepared surgical handover record sheet and necessary instruments, and sent the patient to the operating room.

3.2.3. Identification and Intervention of Psychological Problems

The uncertainty of illness and social isolation are the main reasons for the patients to produce a series of emotional reactions after the patient enter the isolation ward, and the strong emotional reaction causes the body to produce stress response, which is easy to cause anxiety, impatience, pessimism and other negative emotions, resulting in the disorder of autonomic nerve function, the reduction of human immunity, and harmful effect on the outcome and prognosis of the disease [5]. Psychological doctors consult in time, conduct psychological counseling, and explain that rehabilitation training is a gradual process. Under the guidance of medical staff, active exercise can achieve good results. Nursing staff encourage the patient to express his thoughts, listen patiently to the needs, introduce the successful rehabilitation examples of similar diseases in the past, enhance the confidence in rehabilitation, make him actively cooperate with treatment, and improve his psychological disease resistance ability. Nurses should try to communicate with the patient and his families, friends, leaders and other relevant personnel to meet the needs of him as much as possible, so that he can feel the care of his families and friends [6].

3.3. Giving Full Play to the Advantages of Multidisciplinary Team Work on Key Nursing Problems

3.3.1. Disinfection and Isolation Measures

The patient returned from Tanzania and had low fever symptoms before, who was isolated as a suspected case according to the epidemiological investigation. After admission, the patient entered the isolation ward from the special channel and treatment was carried out in a single isolation room. Cleaning workers trained by professional personnel carried out cleaning and disinfection work in the isolation ward. Nurses guided the patient to pour 20,000 mg/L chlorine-containing disinfectant into the bedpan for 2 hours after each defecation and urination, and then pour them into the toilet. Relevant guidelines were formulated to inform the patient. The patient must wear a mask during hospitalization, and nurses also guided the wearing method of the mask and assisted the patient to wear it correctly. The air disinfector runs continuously for 24 hours [7].

3.3.2. Disease-Related Care Measures

After admission, closely monitor and record the vital signs, limb muscle strength, feeling, movement and defecaton and urination, pay attention to the occurrence of hypotension and hyponatremia, and monitor the urine volume and urine specific gravity. Focus on whether the patient has the following clinical symptoms

and complaints: 1) Whether the patient has fever, fatigue, etc. 2) Patients with pneumonia: cough, expectoration, chest tightness, shortness of breath. 3) Patients with nasal congestion, runny nose, sore throat and diarrhea and other symptoms. 4) Whether the patient has dyspnea or hypoxemia, whether there is cyanosis in the nail bed and lips. 5) Whether the vital signs of patients are stable. Report to the doctor in time in case of any abnormality [7].

3.3.3. Functional Exercise

The principle of functional exercise is to start as early as possible, step by step, combine the active and passive, and persist for a long time. Without affecting the fixation, the muscles, tendons, ligaments and joint capsules of the affected limb should be recovered as soon as possible [8]. Specific rehabilitation exercise prescriptions were formulated by the orthopedic nursing staff after the ward round, which were assisted by nursing staff in the isolation ward. During the exercise process, the rehabilitation specialist carried out physical therapy such as low-frequency pulse therapy, and the muscle strength was better than before.

3.3.4. Intermittent Catheterization and Urination Training [9]

Early intermittent catheterization is an important way of bladder training, and is the "gold standard" to assist bladder emptying. Intermittent filling and emptying of bladder contribute to the recovery of bladder reflex. Intermittent catheterization should be started as soon as possible after the patient's vital signs are stable. The specific method is to open the catheter every 4 hours and adjust the amount of drinking water according to the urine volume. After training, the patient has regained the consciousness of urination, and the inflow and outflow has reached a relatively balanced level, so as to pull out the catheter as soon as possible.

3.3.5. Constipation

After spinal cord injury, the nervous function of intestinal tract is damaged, and the colonic peristalsis is decelerated, so that the water absorption is more. In addition, the patient's activity and water intake is reduced, and the stool is harder and more difficult to expel. After the rounds of the nursing staff in the rehabilitation department, massaging the area surrounding anus to pull the anal sphincter is performed [10]. The specific method is to make the patient to take the left lying position and mat treatment towel under his hip, apply paraffin oil to the nurse's index and middle finger, and then stick slowly the index finger into the anus after massage. Next Expand the anus in the directions of 12, 3, 6 and 9 o'clock (suppose the patient's spine is in the direction of the clock at 12 o'clock), 10 times in each direction (take out when there is stool in the process of anal dilatation), and then massage clockwise. At the same time, the patient is instructed to eat more food rich in dietary fiber, fresh fruits and vegetables. The result is that the patient can exclude stool.

3.3.6. Prevention of Pressure Sores

Intermittent decompression can well prevent pressure sores [11]. The applica-

tion of local decompression and various decompression equipment is the key. An air cushion bed was used immediately upon admission. Keeping the bed clean and dry, and turning over regularly during the bed rest every 2 hours is also necessary. We also put the patient in the correct position, change the weight support frequently to reduce the pressure, and use soft pillow, sponge pad and other protective equipment [12]. The axis turning method is adopted when turning the body. One needs to fix the head to make it turn with the shoulder at the same time. Before wearing the neck support, the Anpu patch was applied to the inner side of the neck bracket to reduce the friction force when contacting with the skin. The sacral, heel, iliac crest and other pressure parts were externally coated with Saifurun, and the skin of the patient was well protected.

3.3.7. Cancel Quarantine

The nucleic acid results of COVID-19 for three consecutive times within 14 days after isolation in our hospital were negative (shown in the **Table 3** below), and the patient did not have respiratory tract and other related symptoms, which met the conditions for removing isolation. The medical staff informed the patient of the relevant attention points and knowledge of epidemic prevention and control. The patient was recommended to be transferred to the rehabilitation department for further rehabilitation treatment. The patient in rehabilitation department received treatment such as nerve nutrition, improving circulation, symptomatic relief and supportive treatment, passive joints movement training, hand function training, standing bed training, bladder training, electric acupuncture treatment. His finger flexion and extension abductor strength is restored to level 2, hip flexion strength is restored to level 3, and knee extensor strength is restored to level 4. He could also turn over to both sides independently, and could sit up with a lot of help. The balance of the sitting position could reach level 2. Things are getting better and better.

4. Discussion

At present, the number of newly confirmed cases in several provinces of China has been growing at zero for many days. Great progress has been made in the prevention and control of the COVID-19 in China [13]. Although the risk of an outbreak is low at home, the global COVID-19 situation is still severe. The total number of confirmed cases is over 36 million, and more than 1 million deaths are reported. China is still facing high risk of imported cases. Therefore, prevention and control should not be relaxed under normal circumstances. "External defense input, internal defense rebound" has become the focus of epidemic prevention at present.

Table 3. The nucleic acid results of COVID-19 for three consecutive times within 14 days after isolation in our hospital.

Date	25 July	1 August	7 August
Nucleic acid test results	negative	negative	negative

We apply the multidisciplinary collaboration model throughout the whole nursing process according to active and effective disinfection and isolation measures and perioperative nursing care, especially in observing the changes in the patient's condition, Identification and intervention of psychological problems, rehabilitating exercise, prevention of complications. We have achieved good results, which provide effective experience in admitting patients with COVID-19 and combined with many other diseases or complication. The application of multidisciplinary collaboration model not only improves the treatment effect, reduces the incidence of postoperative complications, improves the satisfaction of patients in hospital, but also promotes the development of nursing teams in various specialties.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Study on the Effect of Web-Based Real-Time Interactive Intervention Teaching Model on Self-Efficacy of Gestational Diabetes Mellitus Patients

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Abstract

Object: To explore the effect of web-based real-time interactive intervention teaching model on self-efficacy of Gestational Diabetes Mellitus (GDM) patients. **Method:** Based on the hospital's antenatal check-up archives from June 2018 to January 2019, patients diagnosed with GDM in the second trimester were randomly divided into the control group (100 cases) and the experimental group (121 cases). Patients in the control group received routine care following the diabetes mellitus one-day outpatient guidance, while patients in the experimental group received social media real-time interactive teaching intervention based on routine care, and accepted a nursing intervention scheme based on knowledge-attitude-practice mode. The knowledge of GDM, self-efficacy and self-management behavior indicators were compared between the two groups. **Results:** After the intervention, the self-efficacy scores, the blood glucose monitoring times and the blood glucose compliance rates of the experimental group were significantly higher than those of the control group ($P < 0.05$). The post-intervention GDM knowledge scores of the experimental group were higher than those of the control group, and the difference was not statistically significant ($P = 0.072$). **Conclusion:** Web-based real-time interactive intervention teaching model can effectively improve the self-efficacy of GDM patients and promote the formation of healthy behaviors.

Keywords

Web-Based, Gestational Diabetes Mellitus, Self-Efficacy, Knowledge-Attitude-Practice Mode

*Both are the first authors.

1. Introduction

Gestational Diabetes Mellitus (GDM) is a pregnancy comorbidity that presented normal before pregnancy yet has different degrees of abnormal glucose metabolism during pregnancy [1]. The International Diabetes Federation (IDF) announced that the global incidence of hyperglycemia during pregnancy in pregnant women aged 20 - 49 in 2019 was 15.8%, of which the incidence of GDM was 13.21% [2]. With the improvement of residents' living standards, the incidence of gestational diabetes in China has increased substantially in the past 10 years, and its prevalence has reached 17.5% [3]. GDM will cause a series of short-term and long-term adverse effects on mothers and children. As women's blood glucose levels increase during pregnancy, their risks of premature delivery, cesarean section, shoulder dystocia or birth injury, preeclampsia, and neonatal hypoglycemia also increase [4] [5] [6]. However, the self-management behavior of patients with GDM is not ideal, and the current level of self-management efficacy can barely adapt to the needs of disease treatment [7] [8]. Studies have shown that good, real-time interactive health education interventions have obvious advantages in the short-term effects of blood glucose control and the long-term effects of self-management efficacy [9] [10]. This study explores the effect of web-based real-time interactive intervention teaching model on the self-management efficacy of GDM patients, in order to promote healthy diet and lifestyle of GDM pregnant women, and to provide clinical guidance for promoting the formation of self-management behaviors in patients with GDM.

2. Materials and Methods

2.1. General Information

Based on the regular antenatal check-ups of our hospital from June 2018 to January 2019, patients diagnosed with GDM in the second trimester of pregnancy were selected as the research subjects, and were randomly divided into 100 cases in the control group and 121 cases in the experimental group. Inclusion criteria: 1) conform to the diagnostic criteria recommended by the *Guidelines for the Diagnosis and Treatment of Diabetes in Pregnancy* (2014) for GDM diagnosis; 2) single pregnancy, with archive file setting up in our hospital and plan to give birth in our hospital; 3) skilled use of mobile social media; 4) no mental illness or severe heart, liver and kidney dysfunction, and no intellectual or speech disorders; 5) informed consent. Exclusion criteria: 1) with severe complications or comorbidity; 2) communication disorders or mental disorders. The pregnant women cases in the control group were 21 - 44 years old, with an average age of (33.96 ± 5.12) years; educational level: 6 cases were at the level of junior high school and below, while 22 were high school, 29 were junior college, and 43 were bachelor and above. The cases in the experimental group were 22 - 43 years old, with an average age of (33.15 ± 5.13) years; educational level: 6 cases were at the level of junior high school and below, 29 cases were high school, 29 cases were junior college, and 57 cases were bachelor degree and above. There was no sig-

nificant difference in age and educational level between the two groups of patients ($P > 0.05$), and they were comparable (Table 1).

2.2. Methods

2.2.1. Interventional Methods

The control group received routine care following the diabetes mellitus one-day outpatient guidance that instructed on the theoretical knowledge, diet, exercise, blood glucose monitoring, etc. The experimental group received social media real-time interactive teaching intervention based on the control group's routine care, and adopted a nursing intervention scheme based on knowledge-attitude-practice mode. Jointly discussed and formulated by an obstetrician, an obstetrical chief nurse and two nurses-in-charge, the nursing intervention scheme was based on the three stages of the "knowledge-attitude-practice" theoretical model, namely acquiring knowledge, generating attitudinal belief, and forming practice. See Table 2 for details.

2.2.2. Observation Indicators

1) Comparison of GDM knowledge scores between the two groups before and after intervention. Self-designed GDM knowledge questionnaire with right-or-wrong questions was used to measure the patient's cognition level of GDM and the treatment. 1 point for each question, and the total score range was 0 - 20 points.

2) Comparison of self-efficacy between the two groups before and after intervention. The diabetes self-efficacy scale developed by Chen Qi *et al.* [11] was used, which contained 20 items and assessed the extent to which respondents believe that they can manage their blood sugar, diet, and exercise levels. The responses were divided into 11 levels, with 0 points for "completely impossible" and 10 points for "completely possible". The total score ranged from 0 to 200 points. The higher the score, the higher the self-efficacy. Score indicator = (the actual score of the sub-scale/the highest possible score of the scale) × 100%. According to the ranking of the score indicators, the self-efficacy was divided into 3 levels: good, fair and poor, where ≥80% was good self-efficacy, 40% - 80% was fair self-efficacy, and ≤40% was poor self-efficacy.

Table 1. Comparison of general data of the two groups of pregnant women.

Group	n =	Age	Educational level
Control Group	100	33.96 ± 5.12	Junior high school and below: 6 High school: 22 Junior college: 29 Bachelor degree and above: 43
Experimental Group	121	33.15 ± 5.13	Junior high school and below: 6 High school: 29 Junior college: 29 Bachelor degree and above: 57
P		>0.05	>0.05

Table 2. Intervention methods of the two groups.

	Intervention variables	Intervention purpose	Time and methods	Details
Control Group		Train GDM patients to complete self-regulation of diet and blood glucose monitoring	Day 1: Face-to-face one-day outpatient health education on diabetes 1) GDM information providing; 2) blood glucose monitoring; 3) diet guidance and recording; 4) exercise guidance.	1) Explain the dangers of GDM; 2) weight management and reasonable diet during pregnancy, experience the breakfast, lunch and snacks customized by the nutrition and diet department of the hospital; 3) exercise during pregnancy, and practice GDM health exercises for half an hour; 4) glucose management guidance, teach GDM patients to monitor blood glucose.
Experimental Group	Knowledge	To enhance GDM patients' awareness of gestational diabetes	Week 1: Face-to-face one-day outpatient health education on diabetes 1) GDM information providing; 2) blood glucose monitoring; 3) diet guidance and recording; 4) exercise guidance.	1) Explain the pathogenesis of GDM and its harmful impact on the mothers and the children; 2) weight management and reasonable diet during pregnancy, experience the breakfast, lunch and snacks customized by the nutrition and diet department of the hospital; 3) exercise during pregnancy, and practice GDM health exercises for half an hour; 4) glucose management guidance, teach GDM patients to monitor blood glucose, explain how to use the mini program in the WeChat group to record and share the information of each meal and blood glucose.
	Attitude	To promote correct beliefs and attitudes for patients with GDM	Weeks 1 - 6: Interact in the WeChat group in real time to engage pregnant women to participate. Twice a week, 1 hour each time.	1) Share popular science articles in WeChat groups on the hazards and effects of GDM, key points of diet control, knowledge of food exchange method, weight management, reference to normal blood glucose, recipe recommendations, etc. 2) encourage patients to monitor their own blood glucose and record their diets, and provide timely feedback on the uploaded diet records and blood glucose values; guide a discussion on topics about diet and exercise once a week, to inspire patients to summarize and analyze their own blood glucose and diet exercise.
	Practice	To guide the formation of healthy behaviors for GDM patients	From the start of intervention to the end of pregnancy: record with WeChat mini program, once a week or once every two weeks.	Instruct the patients to perform self-blood glucose testing on a regular basis (one day of a week or every two weeks), use the WeChat mini program to record meals, and maintain proper exercise until the end of pregnancy.

3) Comparison of self-management behavior, frequency of self-blood glucose monitoring and blood glucose compliance rate between the two groups before and after intervention. In this study, the blood glucose compliance rate was defined as: [the number of blood glucose values that met the criteria of the Chinese *Guidelines for the Diagnosis and Treatment of Diabetes in Pregnancy* (2014)]/(the total number of measurements) ≥80%.

2.2.3. Statistical Methods

Statistical software SPSS 25.0 was used for data processing and statistical analysis. Measurement data were expressed as mean ± standard deviation, and the comparison of indicators between groups was performed by two independent samples t-test and repeated measures analysis of variance.

3. Results

1) The scores of GDM knowledge in the two groups after intervention (Table 3).

2) Self-efficacy scores of the two groups' patients (Table 4).

3) Comparison of self-management behavior indicators between the two groups after intervention (the blood glucose monitoring times, the blood glucose compliance rate, and the value of glycosylated hemoglobin) (Table 5).

4. Discussion

The high incidence of GDM and its adverse effects on mothers and children have made GDM patients' blood sugar management more and more attention. Patients with GDM are the main undertakers of their blood glucose management, so their self-management behavior can change the hyperglycemia situation during pregnancy to a large extent. The levels of GDM patients' blood glucose self-management, such as fine control of diet, implementation of exercise therapy and standardized monitoring of blood glucose, can stabilize blood glucose fluctuations, so that patients can pass the pregnancy smoothly and reduce maternal and child complications [12]. In this study, the experimental group

Table 3. Comparison of the knowledge scores of GDM before and after intervention.

Group	n =	Before intervention	After intervention
Control	100	12.70 ± 3.27	19.26 ± 1.12
Experimental	121	12.46 ± 3.05	19.51 ± 0.96
t		0.557	−1.809
P		>0.05	0.072

Table 4. Comparison of self-efficacy scores.

Group	n =	Scores of self-efficacy
Control	100	104.39 ± 7.30
Experimental	121	108.55 ± 8.28
t		−3.916
P		**<0.001**

Table 5. Comparison of self-management behavior indicators after intervention.

Group	n =	Blood glucose monitoring times		Blood glucose compliance rates (%)	
		1 week after intervention	6 weeks after intervention	1 week after intervention	6 weeks after intervention
Control	100	14.00 ± 4.19	17.98 ± 7.54	72.42 ± 16.72	66.99 ± 20.96
Experimental	121	16.71 ± 5.51	20.92 ± 8.26	80.32 ± 17.89	76.08 ± 28.02

Seeing from the comparison of blood glucose monitoring times and blood glucose compliance rates after intervention between the two groups, the differences between groups and between different time points were statistically significant ($P < 0.05$).

received planned information support in stages under the nursing intervention scheme based on the knowledge-attitude-practice mode. The face-to-face one-day outpatient guidance on diabetes at the first week provided basic targeted information to increase GDM patients' awareness of the disease and their own status. The experimental group in this study scored higher on GDM knowledge than the control group, indicating that the web-based real-time interactive intervention teaching model can effectively enhance GDM patients' disease knowledge.

Self-management efficacy refers to people's belief or confidence in their ability to achieve a behavior goal in the specific field; it is the degree of confidence an individual has to complete a specific behavior and achieve the expected result [13]. If patients with GDM can develop good self-management efficiency, making healthy behaviors the norm in their family, it is bound to have a positive impact on the offspring's lifestyle [14]. In this study, the real-time interaction intervention in the WeChat group lasted for six weeks, twice a week and one hour at a time, which fully mobilized the subjective initiative of the pregnant women. Under the active promotion of the intervener and peers in the same period, it positively promoted the GDM patients to form correct beliefs and attitudes on the disease, and ultimately guided the formation of patients' healthy behaviors. Studies have shown that the improvement of self-efficacy can enhance pregnant women's confidence in childbirth and mobilize the enthusiasm of treatment, thereby conducive to blood glucose control, reducing the occurrence of postpartum complications [15]. In this study, the self-efficacy scores of the experimental group were higher than those of the control group after six weeks of intervention. The difference was statistically significant, indicating that periodical and regular immediate intervention has a positive effect on the improvement of patients' self-management efficiency.

In this study, the two groups of patients had differences in the blood glucose monitoring times and the blood glucose compliance rates at one week after the intervention and six weeks after the intervention. Among them, the blood glucose monitoring times continued to increase with the passage of the intervention time, which shows that the six-week uninterrupted information output has contributed to the improvement of patients' self-management awareness and precise blood glucose control emphasis. In the results of this study, the blood glucose compliance rate decreased with the intervention time. This may be due to the fact that the increase in blood glucose levels that meet the criteria of the Chinese guidelines for the diagnosis and treatment of gestational diabetes mellitus is lower than the increase in the total number of blood glucose measurements. At the same time, there were differences in the blood glucose monitoring times and blood glucose compliance rates between the two groups at each intervention time point, and those of the experimental group was all higher than those of the control group, which shows that the real-time interactive intervention teaching model can continue to effectively promote the formation of self-management behaviors, and improve the GDM pregnant women's follow-up healthy behavior pattern simultaneously. It has important guiding significance for the mainten-

ance of later behavior.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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A Nomogram for Predicting the Severity of COVID-19 Using Laboratory Examination and CT Findings

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Abstract

Background: The outbreak of COVID-19 has a significant impact on the health of people around the world. In the clinical condition of COVID-19, the condition of critical cases changes rapidly with a high mortality rate. Therefore, early prediction of disease severity and active intervention play an important role in the prognosis of severe patients. **Methods:** All the patients with COVID-19 in Taizhou city were retrospectively included and segregated into the non-severe and severe group according to the severity of the disease. The clinical manifestations, laboratory examination results, and imaging findings of the 2 groups were analyzed for comparing the differences between the 2 groups. Univariate and multivariate logistic regression were used for screening the factors that could predict the disease, and the nomogram was constructed. **Results:** A total of 143 laboratory-confirmed cases were included in the study, including 110 non-severe patients and 33 severe patients. The median age of patients was 47 years (range, 4 - 86 years). Fever (73.4%) and cough (63.6%) were the most common initial clinical symptoms. By using the method of multivariate logistic regression, the variables to construct nomogram include age (OR: 1.052, 95% CI: 1.020 - 1.086, $P = 0.001$), body temperature (OR: 2.252, 95% CI: 1.139 - 4.450, $P = 0.020$), lymphocyte count (OR: 1.128, 95% CI: 1.000 - 1.272, $P = 0.049$), ADA (OR: 1.163, 95% CI: 1.023 - 1.323, $P = 0.021$), PaO_2 (OR: 0.972, 95% CI: 0.953 - 0.992, $P = 0.007$), IL-10 (OR: 1.184, 95% CI: 1.037 - 1.351, $P = 0.012$), and bronchiectasis (OR: 3.818, 95% CI: 1.694 - 8.605, $P = 0.001$). The AUC of the established nomogram was 0.877. **Conclusions:** This study analyzed the cases of patients with COVID-19

in Taizhou city and constructed a model to predict the illness severity. When patients showed the features including older age, high body temperature, low lymphocyte count, low ADA value, low PaO_2, high IL-10, and bronchiectasis sign in CT predicts a greater likelihood of severe COVID-19.

Keywords

COVID-19, SARS-CoV-2, Clinical Characteristics, Severity Prediction

1. Background

In December 2019, the first pneumonia case of unknown origin was reported in Wuhan [1] [2] [3], the capital of China's Hubei province. The pathogen was identified as a new enveloped RNA betacoronavirus, which was considered to have developmental similarity with SARS-CoV [4]. The World Health Organization (WHO) named the virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and named the resulting disease as coronavirus disease 2019 (COVID-19). Most of the infected individuals present with acute viral pneumonia, which spreads from person to person [5] [6] [7] [8].

In January 30, 2020, the WHO declared COVID-19 as the sixth public health emergency of international concern (PHEIC). As of March 6, 2020, there were 97,769 laboratory-confirmed cases worldwide [9]. The statistics of SARS-CoV (severe acute respiratory syndrome coronavirus), which appeared in 2003, reported 8422 infected people [10] [11]. In 2012, MERS-CoV (Middle East respiratory syndrome coronavirus) was prevalent only in the Middle East [12] [13] [14] [15]. However, COVID-19 has become a globally widespread disease [9] [16] [17], and the number of confirmed cases continues to rise [18].

According to the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (*Trial Version* 5), COVID-19 can be divided into 4 clinical types [19]. Clinical types are closely related to the prognosis of patients where critical-type patients develop acute symptoms and have a high mortality rate. At present, the severity of the disease is mainly based on patients' symptoms, laboratory examination, and CT performance, and then the clinicians make the adjustment of treatment measures. There are few methods and studies for the prediction of disease severity.

Hence, the purpose of this study was to predict the severity of COVID-19. We collected Taizhou all cure COVID-19 cases and retrospectively analysed the epidemiological characteristics, initial laboratory examination results, and CT images after hospitalisation. We aim to identify factors to construct a model for predicting the severity of COVID-19, for understanding the trend of disease progression in patients with newly diagnosed COVID-19, and for reducing the mortality and improving the prognosis of patients with a high risk of severe COVID-19.

2. Methods

2.1. Study Participants and Design

From January 17 to March 11, 2020, patients were consecutively enrolled in 4 hospitals in Taizhou city. The 4 hospitals include a municipal hospital and 3 county-level hospitals, namely the Taizhou Hospital Enze district, Wenling First People's Hospital, Sanmen People's Hospital, and Tiantai People's Hospital. All the patients were admitted after laboratory confirmation of SARS-CoV-2 infection. After diagnosis, all the patients were transferred to Taizhou Public Health Centre for isolation treatment, and the last patient was discharged from hospital on March 11, 2020 (the deadline for the study).

2.2. Data Source

We obtained electronic medical records and data of all the cured and discharged COVID-19 cases from the 4 hospitals from January 17 to March 11, 2020. The diagnostic criteria were positive result using qPCR detection of nasal swabs and pharyngeal swabs, which was carried out by using a Novel Coronavirus Real Time qPCR Kit, and processed according to the manufacturer's instructions (Shanghai ZJ Bio-Tech Co., Ltd). As all the confirmed diseases in Taizhou were treated at the public health centre of Enze district of Taizhou hospital, the medical records of some patients before admission were provided by the doctors from the respective hospitals. The cases from Wenling People's Hospital, Sanmen People's Hospital, and Tiantai People's Hospital were sent to the Taizhou Hospital researchers by the participants in the hospital. Only laboratory-confirmed cases were included in the study.

All clinical data were reviewed and extracted by a team of experienced respiratory clinicians in Taizhou hospital. The data were recorded in an Excel spreadsheet; if a data is missing, a request is made to the hospital where the participant is located, and the hospital participant then contacts the attending clinician. We extracted recent exposure history, clinical symptoms or signs, and laboratory examination results for admission from the electronic medical record. Imaging examinations included chest X-ray or computed tomography (CT) of the thorax. All the patients who underwent CT scanning were evaluated and reviewed by senior radiologists at Taizhou hospital. Any major differences between the 2 reviewers were resolved by discussion with the third panel of reviewers. All laboratory examinations were performed according to the patients' clinical care needs, including a complete blood count, blood chemical analysis, coagulation test, assessment of liver and kidney function as well as electrolytes, c-reactive protein (CRP), calcitonin, lactate dehydrogenase, lymphocyte factor assay, blood gas analysis, and creatine kinase measurements.

2.3. Study Definitions and Criteria

We segregated all the patients into severe group and non-severe group according to the *Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia* (*Trial*

Version 5) released by the National Health Commission & State Administration of Traditional Chinese Medicine [19]. The severe group included the serious and critical types, while the non-severe group included the mild and moderate types. The mild type was defined as having mild clinical symptoms with no signs of pneumonia based on imaging results. The moderate type was defined as having symptoms such as fever, respiratory tract symptoms, and the appearance of pneumonia based on imaging results. The serious type was defined based on the following conditions: 1) respiratory distress with respiratory rate (RR) > 30/min; 2) oxygen saturation < 93% at rest; and 3) arterial blood oxygen partial pressure ($Pa0_2$)/oxygen concentration ($Fi0_2$) < 300 mmHg (1 mmHg = 0.133 KPa). The critical type was defined based on any of the following conditions: 1) respiratory failure and the need for mechanical ventilation; 2) shock; and 3) organ failure that requires intensive care unit (ICU) care.

The date of exposure refers to the earliest date of exposure to a source of transmission (people in Wuhan or confirmed patients). The incubation period was defined as the time interval between the potential earliest date of exposure to the source of transmission and the earliest date of occurrence of symptoms (clinical symptoms such as cough and fever). The specific contact date (if the date was unclear, the case was excluded from the analysis) was recorded, and the incubation period was calculated based on the specific information of the exposure date. Treatment delay indicates the time between the onset of symptoms and hospitalisation. Body temperature under the armpit ≥37.5˚C was defined as fever.

2.4. Laboratory Confirmation

All cases were confirmed by the Zhejiang Center for Disease Control and Prevention (Zhejiang CDC). The nucleic acid extraction was carried out with the kit (Biogas, Nkilier Technology Co. LTD, Shenzhen, China) recommended by the Chinese Center for Disease Control and Prevention (China CDC). RT-PCR assays were performed in accordance with the protocol established by the WHO, and nucleic acid sequencing was performed using NGS (next-generation sequencing) technology.

2.5. Statistical Analysis

We used Microsoft corp. EXCEL, version 2019 (Microsoft Corporation, American), R software, version 3.5.2 (MathSoft company, American), and MedCalc for Windows, version 15.0 (MedCalc Software, Ostend, Belgium), for data processing and analysis. Independent *t* sample test was used for comparing the difference between the 2 groups of continuous variables. The differences between the 2 groups were compared by the chi-square test or Fisher's exact test. Logistic regression analysis was performed on the indicators with statistically significant differences between the 2 groups ($P < 0.05$). The R software was used for generating the nomogram and MedCalc software was used for generating the receiver operating characteristic (ROC) curve. Test results with $P < 0.05$ was considered

statistically significant.

Ethical approval

The retrospective multicentre cohort study was approved by the ethics review committee of Taizhou Hospital, Sanmen People's Hospital, Wenling First People's Hospital, and Tiantai People's Hospital, and the written informed consent was waived.

3. Results

3.1. Demographic Characteristics of the Patients

As of March 11, 2020, a total of 146 confirmed patients in Taizhou were transferred to isolation hospitals and were discharged after the treatment. Three cases were not included in this study owing to the loss of the CT images of the first time on admission. We obtained basic information, clinical data, and CT images of 143 patients (96.6%), among whom 66 were women (46.2%), and 77 were men (53.8%). The demographic and clinical characteristics of the patients are shown in Table 1. On admission, the degree of severity of COVID-19 was categorized as non-severe in 110 patients and severe in 33 patients. Of all the patients, 60 patients (42.0%) had contacts with a confirmed patient, 70 (49.0%) had contacts with a person in the Wuhan area, 4 (2.8%) had contacts with both a confirmed patient and a person in the Wuhan area, and 9 (6.3%) had an unclear contact history. The median age of all the patients was 47 years (range, 4 - 86 years), 56.8% were aged 30 - 60 years. The median age of the non-severe patients was 44.5 years (range, 4 - 80 years), while the median age of the severe patients was 55.0 years (range, 27 - 86 years). 129 patients (90.2%) had a history of smoking, including 100 patients (90.9%) in the non-severe group and 29 patients (87.9%) in the severe group.

Table 1. Clinical characteristics of the study patients, according to disease severity.

	Overall (n = 143)	Non-severe (n = 110)	Severe (n = 33)
Age (years)			
Median (range)	47.0 (4 - 86)	44.5 (4 - 80)	55.0 (27 - 86)
<38	34 (23.8%)	31 (32.7%)	3 (0.9%)
38 - 48	43 (30%)	36 (32.7%)	7 (21.2%)
49 - 60	34 (23.8%)	26 (26.3%)	8 (24.2%)
>60	32 (22.4%)	17 (15.5%)	15 (45.5%)
Gander			
Female	66 (46.2%)	52 (47.3%)	14 (42.4%)
Male	77 (53.8%)	58 (52.7%)	19 (57.6%)
Smoking			
No	129 (90.2%)	100 (90.9%)	29 (87.9%)
Yes	13 (9.1%)	9 (8.2%)	4 (12.1%)
Unknown	1 (0.7%)	1 (0.9%)	0 (0%)

Continued

Contact history			
The history of contact with confirmed patients	60 (42.0%)	46 (41.8%)	14 (42.4%)
The history of contact with epidemic area	70 (49.0%)	54 (49.1%)	16 (48.5%)
Unknown	9 (6.3%)	6 (5.5%)	3 (9.1%)
Both	4 (2.8%)	4 (3.6%)	0 (0%)
Temperature (˚C)			
<37.5	1 (0.7%)	1 (0.9%)	0 (0%)
37.5 - 38	7 (4.9%)	7 (6.4%)	0 (0%)
38 - 38.5	39 (27.3%)	29 (26.4%)	10 (30.3%)
38.5 - 39	26 (18.2%)	19 (17.3%)	7 (21.2%)
39 - 40	32 (22.4%)	20 (18.2%)	12 (36.4%)
>40	1 (0.7%)	1 (0.9%)	0 (0%)
Unknown	37 (25.9%)	33 (30.0%)	4 (12.1%)
Clinical symptoms			
Fever	105 (73.4%)	76 (53.1%)	29 (20.1%)
Coughing of phlegm	41 (28.7%)	30 (27.3%)	11 (33.3%)
Dry cough	42 (29.4%)	30 (27.3%)	12 (36.4%)
Yellow sputum	8 (5.6%)	6 (5.5%)	2 (6.1%)
Sore throat	15 (10.5%)	12 (10.9%)	3 (9.1%)
Nasal obstruction	8 (5.6%)	8 (7.3%)	0 (0%)
Muscle soreness	14 (9.8%)	11 (10.0%)	3 (9.1%)
Weak	37 (25.9%)	31 (28.2%)	6 (18.2%)
Chest distress	25 (17.5%)	17 (15.5%)	8 (24.2%)
Coexisting disorders			
hypertension	20 (14.0%)	15 (13.6%)	5 (15.2%)
diabetes	12 (8.4%)	7 (6.4%)	5 (15.2%)
COPD	3 (2.1%)	2 (1.8%)	1 (3.0%)
The incubation period (days)			
<3	3 (2.1%)	3 (2.7%)	0 (0%)
3 - 6	10 (7%)	9 (7.3%)	1 (3.0%)
6 - 9	10 (7%)	9 (8.1%)	1 (3.0%)
9 - 12	6 (4.2%)	3 (2.7%)	3 (9.1%)
>15	4 (2.8%)	4 (3.6%)	0 (0%)
Unknown	110 (76.9%)	82 (74.5%)	28 (84.8%)
Treatment delay			
<1	49 (34.3%)	8 (24.2%)	41 (37.3%)
1 - 2	40 (28.0%)	8 (24.2%)	32 (29.1%)
2 - 5	22 (15.4%)	6 (18.2%)	16 (14.5%)
5 - 10	16 (11.2%)	7 (21.2%)	9 (8.2%)
>10	2 (1.4%)	2 (6.1%)	0 (0%)
Unknown	14 (9.8%)	2 (6.1%)	12 (10.9%)

The mean incubation period was 6.9 days (standard deviation [SD], 3.472 days), and the mean treatment delay period was 3.0 days (SD, 2.631 days). Fever (73.4%) was the most common symptom. A total of 91 patients (63.6%) developed cough: sputum (28.7%), yellow sputum (5.6%), and dry cough (29.4%). Sore throat (10.5%), nasal congestion (5.6%), muscle soreness (9.8%), and chest tightness (17.5%) were relatively few. Of all the patients, 24.5% had at least one coexisting illness (hypertension and/or chronic obstructive pulmonary disease). The average body temperature of the patients was 38.0˚C (range, 37˚C - 39˚C; SD, 3.741˚C), and only 1 case (0.7%) had a high fever (>40˚C).

3.2. Laboratory Examination Results of the Two Groups

As some of the patients were first admitted to the county hospital, some laboratory tests were not carried out owing to the conditions. A total of 123 cases was included for the analysis of laboratory examination results, and those without such examination were recorded as UNKOWN. There were 28 cases in the severe group and 95 cases in the non-severe group. Table 2 shows the details of the laboratory results of all the cases. In the non-severe group, except for the increase in blood glucose level (14 ± 60 mmol/L), the decrease of serum albumin (39 ± 5.2 g/L), erythrocyte sedimentation rate (35 ± 24 μmol/L), and serum sodium (130 ± 25 mmol/L), and the increase of CRP (15 ± 19 mg/L) and amyloid A (190 ± 330 mg/L) were observed. All other test results were within the normal range (Table 2).

Table 2. Laboratory findings of patients with COVID-19 on admission to hospital.

	Normal Range	Overall (n = 123)	Non-Severe (n = 95)	Severe (n = 28)
Lymphocyte count, $\times 10^9$/L	1.1 - 3.2	1.2 (±0.52)	1.3 (±0.52)	0.91 (±0.43)
$<1.1 \times 10^9$		43 (34.96%)	27 (28.42%)	16 (57.14%)
$1.1 - 3.2 \times 10^9$		67 (54.47%)	60 (63.16%)	7 (25%)
unknown		13 (10.57%)	8 (8.42%)	5 (17.86%)
Erythrocyte sedimentation rate (ESR), umol/L	59 - 104	38 (±24)	35 (±24)	47 (±24)
<59		68 (55%)	56 (59%)	12 (43%)
59 - 104		12 (10%)	8 (8%)	4 (14%)
Unknown		43 (35%)	31 (33%)	12 (43%)
Blood glucose, mmol/L	3.9 - 6.11	13 (± 53)	14 (± 60)	9.1 (± 5.1)
3.9 - 6.11		44 (36%)	36 (38%)	8 (29%)
>6.11		62 (50%)	47 (49%)	15 (54%)
Unknown		17 (14%)	12 (13%)	5 (18%)
Aspartate aminotransferase, U/L	15 - 40	30 (±17)	26 (±11)	40 (±28)
15 - 40		91 (74.0%)	73 (80.2%)	18 (19.8%)
>40		17 (13.8%)	10 (57.8%)	7 (42.2%)

Continued

Creatine kinase (CK), U/L	38 - 285	99 (±93)	83 (±69)	150 (±130)
38 - 285		85 (69%)	68 (72%)	17 (61%)
>285		13 (11%)	9 (9%)	4 (14%)
Unknown		25 (20%)	18 (19%)	7 (25%)
ADA, U/L	<20	13 (±3.6)	13 (±3.5)	15 (±3.8)
Lactic acid dehydrogenase, U/L	80 - 285	240 (±140)	200 (±100)	350 (±180)
80 - 285		72 (59%)	65 (68%)	7 (25%)
>285		21 (17%)	8 (8%)	13 (46%)
Unknown		30 (24%)	22 (23%)	8 (29%)
Albumin, g/L	40 - 55	38 (±5.2)	39 (±5.2)	35 (±4.0)
<40		16 (13%)	9 (9%)	7 (25%)
40 - 55		31 (25%)	29 (31%)	2 (7%)
Unknown		76 (62%)	57 (60%)	19 (68%)
Na, mmol/L	137 - 147	130 (±22)	130 (±25)	140 (±3.7)
<137		37 (30%)	29 (31%)	8 (29%)
137 - 147		69 (56%)	54 (57%)	15 (54%)
Unknown		17 (14%)	12 (13%)	5 (18%)
Mg, mmol/L	0.75 - 1.02	3.8 (±17)	4.7 (±19)	0.89 (±0.096)
<0.75		10 (8%)	8 (8%)	2 (7%)
CRP, mg/L	<8	20 (±24)	15 (±19)	35 (±31)
0 - 8		51 (41%)	44 (46%)	7 (25%)
>8		51 (41%)	36 (38%)	15 (54%)
Unknown		21 (17%)	15 (16%)	6 (21%)
Glomerular filtration rate (GFR), ml/min	NA	91 (±21)	94 (±19)	82 (±26)
Amyloid A	0 - 10	250 (±360)	190 (±330)	430 (±420)
0 - 10		21 (17%)	19 (20%)	2 (7%)
>10		79 (64%)	59 (62%)	20 (74%)
fibrinogen, s	2.0 - 4.0	3.9 (±1.4)	3.7 (±1.4)	4.5 (±1.3)
>4		30 (24%)	17 (18%)	13 (46%)
0 - 4		60 (49%)	51 (54%)	9 (32%)
D dimer level, g/L	0 - 0.5	0.40 (±0.59)	0.35 (±0.58)	0.54 (±0.63)
PaO_2, mmHg	83 - 108	94 (±31)	99 (±33)	83 (±24)
<83		36 (29%)	23 (24%)	13 (46%)
83 - 108		35 (28%)	28 (29%)	7 (25%)
>108		21 (17%)	18 (19%)	3 (11%)
Unknown		31 (25%)	26 (27%)	5 (18%)
Oxygen concentration, %	NA	26 (±13)	25 (±14)	27 (±11)
0 - 21		61 (50%)	51 (54%)	10 (36%)

Continued

>21		31 (25%)	18 (19%)	13 (46%)
Unknown		31 (25%)	26 (27%)	5 (18%)
Myoglobin, ng/ml,	12 - 75	46 (±56)	35 (±41)	84 (±80)
<12		7 (6%)	6 (6%)	1 (4%)
12 - 75		54 (44%)	45 (47%)	9 (32%)
>75		12 (10%)	5 (5%)	7 (25%)
IL-10, pg/ml	0.1 - 5.0	5.2 (±5.2)	4.0 (±2.5)	9.4 (±9.2)
0 - 5		56 (46%)	49 (52%)	7 (25%)
>5		28 (23%)	17 (18%)	11 (39%)
CD3 absolute value, /uL	770 - 2041	720 (±450)	790 (±460)	490 (±330)
<770		28 (23%)	19 (20%)	9 (32%)
770 - 2041		17 (14%)	15 (16%)	2 (7%)
CD4 absolute value, /μL	414 - 1123	440 (±260)	490 (±260)	290 (±200)
<414		26 (21%)	18 (19%)	8 (29%)
414 - 1123		19 (15%)	16 (17%)	3 (11%)
CD8 absolute value--/μL	238 - 874	290 (±180)	330 (±180)	190 (±130)
<238		22 (18%)	15 (16%)	7 (25%)
238 - 874		23 (19%)	19 (20%)	4 (14%)

In the severe group, following parameters showed a decreased value: lymphocyte count decreased ((0.91 ± 0.43) $\times 10^9$), erythrocyte sedimentation rate (38 ± 24 μmol/L), serum albumin (130 ± 25 g/L), glomerular filtration rate (82 ± 26 mL/min), arterial blood oxygen partial pressure (83 (± 24) mmHg), calcitonin level (0.086 ± 0.090 μg/L), total CD3 value (56 ± 13%), absolute CD4 value (290 ± 200/μL), and absolute CD8 value (190 ± 130/μL). Following parameters showed an increased value in the severe group: blood glucose level (13 ± 53 mmol/L), lactate dehydrogenase level (350 ± 180 U/L), CPR level (35 ± 31 mg/L), amyloid protein A level (430 ± 420), fibrinogen detection value (4.5 ± 1.3 s), D dimmer level (0.54 ± 0.63 g/L), pH level (7.8 ± 2.0), myoglobin (84 ± 80 ng/mL), IL-10 (9.4 ± 9.2 pg/mL), C1q (240 ± 38 mg/L), PT (16 ± 19 s), absolute CD3 value (490 ± 330/μL). Other test results were within the normal range.

3.3. CT Manifestations of the Two Groups

Five (3%) CT images could not be evaluated owing to poor respiratory artefact quality. CT images of 138 (97%) patients at admission were obtained. Among them, 34 patients were severe (31%) and 104 patients were non-severe (75%). The CT findings of the two groups of cases are shown in Table 3. Lesions in 135 patients (98%) were mainly distributed in the external or subpleural of the lung; 37 patients (27%), middle or inner zone of lung; and 34 patients (25%), both. Among them, the lesions in the middle or inner band of the lungs were more

Table 3. CT Manifestations of patients infected with COVID-19 admission to hospital.

	Overall	Non-Severe	Severe	*P*-value
	(n = 138)	(n = 104)	(n = 34)	
Peripheral or subpleural	135 (98%)	102 (98%)	33 (97%)	
Middle or inner band	37 (27%)	21 (20%)	16 (47%)	0.00441
both	34 (25%)	19 (18.3)	15 (44%)	
Shape				
Paving stone shape	21 (32%)	15 (15%)	6 (18%)	
Mass	51 (81%)	35 (34%)	16 (47%)	
Patchy	24 (40%)	16 (16%)	8 (24%)	
Strip shape	7 (9%)	6 (6%)	1 (3%)	
Honeycomb shape	8 (12%)	6 (6%)	2 (6%)	
Small patchy	58 (68%)	52 (50%)	6 (18%)	
Lung segment shape	4 (12%)	0	4 (12%)	
Irregular	4 (12%)	0	4 (12%)	
Nodular	4 (3.88%)	4 (3.88%)	0	
Ground glass density	37 (27%)	30 (29%)	7 (21%)	0.325
Mixed Density	87 (63%)	62 (60%)	25 (74%)	
Solid Density	14 (10%)	12 (12%)	2 (6%)	
The edge				
clear	21 (15%)	16 (15%)	5 (15%)	
unclear	117 (85%)	88 (85%)	29 (85%)	
CT signs				
consolidation	66 (48%)	43 (41%)	23 (68%)	0.0136
bronchial inflation	63 (46%)	43 (41%)	20 (59%)	0.0015
Bronchiectasis	65 (47%)	41 (39%)	24 (71%)	0.00305
Blood vessels penetrated the lesion	57 (41%)	42 (40%)	15 (44%)	0.855
distribution along the vascular bundle	83 (60%)	64 (62%)	19 (56%)	0.702
Adjacent vascular widening	72 (52%)	55 (53%)	17 (50%)	0.925
Septal thickening	58 (42%)	41 (39%)	17 (50%)	0.376
Fibrosis	42 (30%)	29 (28%)	13 (38%)	0.081
Accompanying signs				
Cavity or calcification				
Non	137 (99%)	103 (99%)	34 (100%)	
Yes	1 (1%)	1 (1%)	0 (0%)	
Lymphadenectasis				
Non	134 (97%)	102 (98%)	32 (94%)	0.545
Yes	4 (3%)	2 (2%)	2 (6%)	

Continued

Pleural effusion				
Non	135 (98%)	103 (99%)	32 (94%)	0.303
Yes	3 (2%)	1 (1%)	2 (6%)	
Chronic bronchitis				
Non	132 (96%)	100 (96%)	32 (94%)	0.983
Yes	6 (4%)	4 (4%)	2 (6%)	
Emphysema or Pulmonary bullous				
Non	133 (96%)	101 (97%)	32 (94%)	0.777
Yes	5 (4%)	3 (3%)	2 (6%)	

commonly observed in the severe patients (47% vs 20%). Mass (81%) was the most common lesion shape followed by patchy (68%). Irregularity in the shapes of the lung segments was observed only in severe patients, while the nodular shape was observed only in non-severe patients. Most of the lesions presented with mixed density (63%).

In 60% of the CT images, the lesion was distributed along the pulmonary bronchial tree, and in 62% of the CT images, the lesion was adjacent to vasodilation. Fifty-two percent of the CT images showed interlobular septal thickening, and 30% of the CT images showed fibrous foci. Other concomitant signs such as cavitation or calcification (1%), enlarged lymph nodes (3%), pleural effusion (2%), chronic bronchitis (4%), emphysema, or pulmonary bullous (4%) were rare. Consolidation (68% vs 41%), bronchial inflation signs (59% vs 41%), and bronchiectasis (71% vs 39%) were more common in the severe group.

3.4. Results of Univariate Logistic Regression Analysis Predicting the Severity of COVID-19 Patients

Univariate logistic regression was performed for all the collected variables, and the results are shown in Table 4. For all the factors such as clinical characteristics, laboratory results, and CT findings, the variables associated with the severity of COVID-19 were age (Odds ratio [OR]: 1.052, 95% confidence interval [CI]: 1.020 - 1.086, $P = 0.001$), days from the symptom onset to hospitalisation (OR: 1.213, 95% CI: 1.034 - 1.939, $P = 0.016$), days from the symptom onset to diagnosis (OR: 1.213, 95% CI: 1.084 - 1.357, $P < 0.001$), body temperature (OR: 2.252, 95% CI: 1.139 - 4.450, $P = 0.020$), Neutrophil count (OR: 0.087, 95% CI: 0.026 - 0.274, $P < 0.001$), Lymphocyte count (OR: 1.128, 95% CI: 1.000 - 1.272, $P = 0.049$), IgM (OR: 2.226, 95% CI: 1.015 - 4.883, $P = 0.046$), ADA (OR: 1.163, 95% CI: 1.023 - 1.323, $P = 0.021$), albumin (OR: 0.847, 95% CI: 0.725 - 0.988, $P <0.035$), CRP (OR: 1.024, 95% CI: 1.007 - 1.042, $P = 0.006$), Glomerular filtration rate (OR: 0.965, 95% CI: 0.942 - 0.988, $P = 0.004$), amyloid A (OR: 1.002, 95% CI: 1.001 - 1.003, $P = 0.001$), PCT (OR: 1.43E+11, 95% CI: 1334.315 - 1.53E+19, $P = 0.006$), PaO_2 (OR: 0.972, 95% CI: 0.953 - 0.992, $P = 0.007$), oxygen concentration (OR: 1.027, 95% CI: 1.001 - 1.053, $P = 0.044$), oxygenation index (OR:

Table 4. Univariate logistic regression results predicting severity of COVID-19.

Variable	Odds Ratio	Lower	Upper	*P* value
Age	1.052397	1.019954	1.085873	0.001391
Gender	0.716981	0.33105	1.552824	0.398768
Smoke	1.448029	0.417094	5.027131	0.559917
Contact1	0.9	0.417764	1.938894	0.787878
Contact2	0.882353	0.411933	1.889984	0.747415
Days1	1.195852	1.033785	1.383326	0.016078
Days2	1.212778	1.083784	1.357125	7.73E−04
Fever	2.646341	0.858115	8.161055	0.09033
Temperature	2.25173	1.139284	4.450414	0.019538
Days3	1.115935	0.966888	1.287958	0.133713
Cough	1.710616	0.707724	4.134677	0.233169
Sputum	1.222222	0.534092	2.79695	0.634723
Sore Throat	0.765625	0.203181	2.885017	0.693161
Nasal Congestion	6.85E−08	0	Inf	0.99059
Muscle Soreness	0.84375	0.221514	3.213852	0.803366
Weak	0.551724	0.208304	1.461324	0.23144
Chest Congestion	1.893665	0.756532	4.740007	0.172581
Diarrhea	1.053763	0.316912	3.503867	0.931923
Headache	2.125	0.646991	6.979424	0.214117
Dizziness	0.9375	0.242985	3.617126	0.925361
Basic Diseases	1.118012	0.499822	2.500796	0.785943
Hypertension	1.055556	0.35412	3.146385	0.922706
Diabetes	2.452381	0.725797	8.286306	0.148723
WBC	1.114387	0.981275	1.265557	0.095174
RBC	0.687443	0.323418	1.461197	0.329977
Hb	0.986271	0.961506	1.011673	0.286656
Hematocrit	1.011476	0.980254	1.043694	0.475669
PLT	0.997789	0.991605	1.004012	0.485326
L	0.086924	0.02757	0.274063	3.06E−05
Ratio of Monocytes	0.141741	0.004924	4.080115	0.254407
N	1.128092	1.00055	1.271893	0.04896
ESR	1.0164	0.997625	1.035529	0.087266
Creatinine	1.014157	0.995714	1.032941	0.133283
Urea	1.020293	0.956143	1.088747	0.544277
BG	0.997512	0.98417	1.011034	0.716888
ALT	1.008354	0.991145	1.025861	0.343522

Continued

Creatine Kinase	1.031699	1.003659	1.060524	0.026436
LAD	1.004959	1.00054	1.009396	0.027792
LDH	1.009157	1.003211	1.015139	0.002501
IgG	0.99228	0.948544	1.038034	0.736158
IgA	0.587786	0.328416	1.051995	0.073569
IgM	2.226405	1.015156	4.882874	0.04577
C3	0.525075	0.076438	3.606887	0.512329
C4	11.63921	0.51351	263.8143	0.12322
ADA	1.163198	1.022728	1.322962	0.021323
Triglyceride	1.008518	0.635767	1.599814	0.971257
Total Cholesterol	0.952982	0.731007	1.24236	0.721871
Albumin	0.84665	0.725305	0.988296	0.034934
Total Bilirubin	1.000508	0.928329	1.078299	0.989395
Direct Bilirubin	1.095907	0.932036	1.288589	0.267757
Indirect Bilirubin	1.03091	0.915937	1.160314	0.613865
K	0.97669	0.830217	1.149005	0.77602
Na	1.005811	0.980137	1.032159	0.660513
Cl	0.99758	0.913238	1.089713	0.957136
Mg	0.120206	0.003512	4.113869	0.239869
P	0.667578	0.209464	2.127617	0.494414
CRP	1.024328	1.007001	1.041952	0.005753
Ca	0.300189	0.047835	1.883842	0.199096
GFR	0.96458	0.941504	0.988221	0.003511
Amyloid	1.001978	1.000766	1.003192	0.001374
C1q	1.008992	0.996395	1.021747	0.162561
CK-MB	1.234022	0.930305	1.636894	0.144623
PT	1.081185	0.873797	1.337794	0.472522
APTT	1.059444	0.963819	1.164557	0.23153
TT	0.995323	0.788852	1.255834	0.968472
Fibrinogen	1.430012	1.025764	1.993573	0.034856
D-D	1.745173	0.788434	3.862884	0.169564
INR	116.4343	0.215575	62887.33	0.13835
PCT	1.43E+11	1334.315	1.53E+19	0.006474
Blood Lactate	1.436125	0.81993	2.515405	0.205621
PH	1.108846	0.84153	1.461076	0.46289
$PaCO_2$	0.960499	0.918259	1.004683	0.079025
PaO_2	0.972351	0.952754	0.992351	0.006952
Oxygen concentration	1.026528	1.000762	1.052959	0.043523

Continued

Oxygenation Index	0.991652	0.987728	0.995591	3.41E−05
Serum Troponin	0.566605	0.002456	130.7373	0.837862
Myoglobin	1.011143	1.002275	1.020089	0.013678
TCD3 (%)	0.993133	0.970569	1.016221	0.556758
TCD4 (%)	0.986364	0.947917	1.026371	0.498528
TCD8 (%)	0.957084	0.903873	1.013426	0.132844
IL2	0.957149	0.821552	1.115126	0.574176
IL4	0.831517	0.501285	1.379297	0.474885
IL6	1.021095	0.99971	1.042937	0.053222
IL10	1.183976	1.037356	1.351319	0.01229
TNF	1.212997	0.853367	1.724185	0.281837
IFN	0.985827	0.920521	1.055767	0.683149
CD3	0.997504	0.995598	0.999413	0.010416
CD4	0.994224	0.989734	0.998735	0.012134
CD8	0.992234	0.986427	0.998076	0.009246
CD19	0.992116	0.983001	1.001316	0.092823
CD15	0.998545	0.994025	1.003085	0.529286
BCD	1.014728	0.977778	1.053074	0.439789
NK	1.045479	0.985567	1.109034	0.139644
CD4 (%)	0.969968	0.911867	1.03177	0.33327
CD8 (%)	0.956199	0.889725	1.027638	0.223089
CD4+CD8 (%)	0.988063	0.873836	1.117222	0.848072
Middle or Inner Band	3.178571	1.398358	7.225127	0.005775
Morphology	1.154643	0.920286	1.448681	0.214134
Density	1.692402	0.860912	3.326964	0.127087
Homogeneousness	1.034294	0.433926	2.465312	0.939352
Margin	1.416667	0.442968	4.530676	0.557063
Consolidation	3.103175	1.398634	6.88507	0.005351
Bronchial Inflation	1.850291	0.858916	3.985927	0.116055
Bronchiectasis	3.818182	1.694264	8.604628	0.00123
Blood vessels penetrated the lesion	1.079365	0.495782	2.349881	0.847426
Distribution along the vascular bundle	0.678571	0.314129	1.465829	0.323749
Adjacent vascular widening	0.989583	0.46112	2.123691	0.978558
Septal Thickening	1.417202	0.65672	3.058319	0.374278
Fibrosis	1.457271	0.643938	3.297897	0.366163

Note. Contact1: The history of contact with confirmed patients; Contact2: The history of contact with epidemic area; Days1: The incubation period (days); Days2: Treatment delay (days); Days3: Course of the disease (days).

0.992, 95% CI: 0.988 - 0.996, $P < 0.001$), myoglobin (OR: 1.011, 95% CI: 1.002 - 1.020, $P = 0.014$), IL-10 (OR: 1.184, 95% CI: 1.037 - 1.351, $P = 0.012$), consolidation (OR: 3.103, 95% CI: 1.399 - 6.885, $P = 0.005$), and bronchiectasis (OR: 3.818, 95% CI: 1.694 - 8.605, $P = 0.001$).

3.5. To Construct A Clinical-Image Nomogram for the Prediction of Severe COVID-19.

All the variables with $P < 0.05$ were screened for multivariable logistic regression. Table 5 and Figure 1 show the variables selected for predicting severe COVID-19 were age (OR: 1.03, 95% CI: 0.99 - 1.07, $P = 0.1565011$), body temperature (OR: 2.28, 95% CI: 1.01 - 5.18, $P = 0.0480145$), Lymphocyte count (OR: 0.11, 95% CI:0.03 - 0.38, $P = 0.0006512$), ADA (OR: 1.27, 95% CI: 1.08 - 1.49, $P = 0.0037539$), PaO_2 (OR: 0.98, 95% CI: 0.95 - 0.99, $P = 0.0511345$), IL-10 (OR: 1.15, 95% CI: 0.99 - 1.34, $P = 0.063646$), bronchiectasis (OR: 5.25, 95% CI: 1.77 - 5.62, $P = 0.0028594$). The final equation is: Nomoscore = 34.663 + Age × 0.028 + Temperature × 0.826 + L × −2.250 + ADA × 0.239 + PaO_2 × −0.023 + IL-10 × 0.143 + Bronchiectasis × 1.659. The established nomogram demonstrates in Figure 2 that clinicians can quickly obtain Nomoscore of a newly confirmed patient based on this figure to determine the likelihood that the patient will develop severe COVID-19.

Table 5. Multivariate logistic regression results predicting severity of COVID-19.

Variable	Odds Ratio	95%CI	*p*-value
Age	1.03	[0.99;1.07]	0.156501
Temperature	2.28	[1.01;5.18]	0.048015
L	0.11	[0.03;0.38]	0.000651
ADA	1.27	[1.08;1.49]	0.003754
PaO_2	0.98	[0.95;0.99]	0.051135
IL-10	1.15	[0.99;1.34]	0.063646
Bronchiectasis	5.25	[1.77;5.62]	0.002859

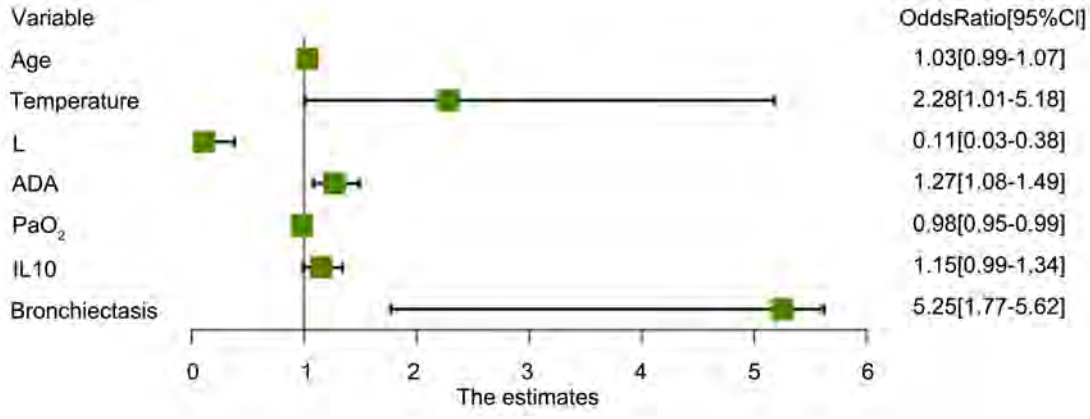

Figure 1. Multivariate logistic regression results predicting severity of COVID-19.

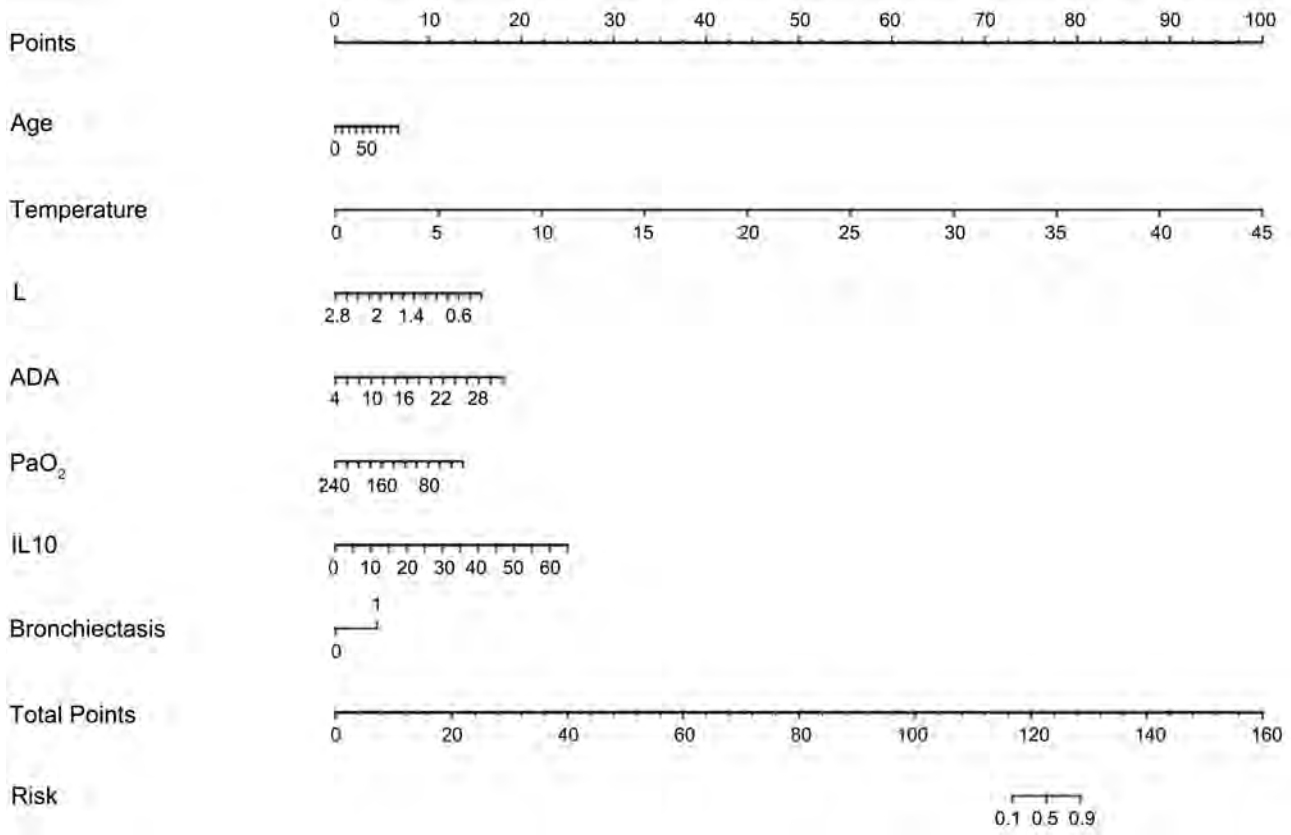

Figure 2. The nomogram for predicting severe COVID-19. According to the patient's age, body temperature, lymphocyte count, ADA value, PaO_2 value, IL-10 value, and whether bronchiectasis was present, the corresponding score was found by perpendicular to the first horizontal line. The probability of predicting severe COVID-19 is obtained by perpendicular the total score to the last horizontal line.

The constructed equation was used for drawing the ROC (**Figure 3**), with the area under the curve being 0.877. The Youden index was used for determining the optimal threshold, and the corresponding sensitivity and specificity were 74.29% and 82.73%, respectively.

4. Discussion

In this retrospective study, by analysing the medical history, clinical information, laboratory examination and CT images of COVID-19 patients who had cured and discharged from hospital, we found some factors related to the severity of the disease, such as age, body temperature, Lymphocyte count, ADA, PaO_2, IL-10, bronchiectasis, and established a stable nomogram. The nomogram established by us was highly sensitive and specific (74.29%, 82.73%). Clinicians could use this nomogram to predict the severity of COVID-19 patients newly diagnosed with a simple and feasible operation.

In the early stage of the COVID-19 outbreak, the severity of COVID-19 is judged mainly based on real-time clinical symptoms, laboratory examination, and imaging manifestations of the patient, which may lead to delayed treatments to some extent. Most of the patients in China have been cured and discharged

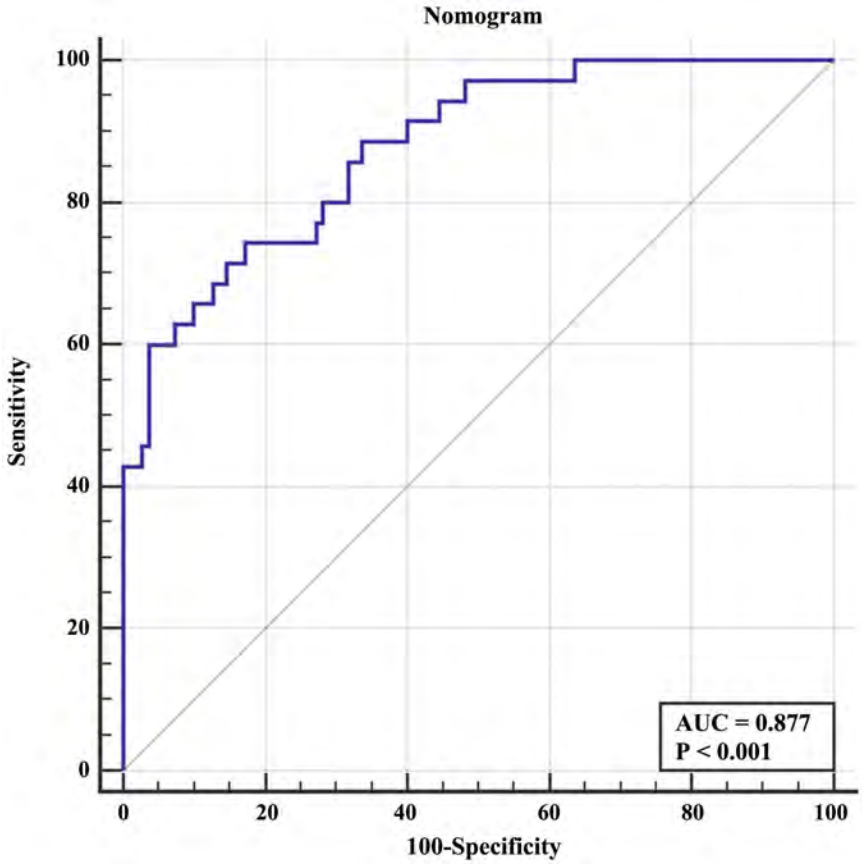

Figure 3. The receiver operating characteristic (ROC) curve of the nomogram predicting severe COVID-19.

from the hospital, so Chinese doctors have accumulated some experience for the diagnosis and treatment of COVID-19 [20] [21] [22] [23].

42% of the patients have been living in Wuhan for a long time or have been to Wuhan or had contact with people returning from Wuhan. This result was similar to that of other studies [24], which contact history was an important factor in the diagnosis of COVID-19. Our study also found that the average age of COVID-19 infected patients was 47.0 years (range, 4 - 86 years), which was similar to the findings of a previous study [20] [24]. The results of this study showed no statistical difference between men and women, but the study by Chen Nanshan *et al.* [25] found that the proportion of men was higher than that of women; hence, more data are needed for confirming the accuracy of this result. Most of the patients (62.3%) went to the hospital within 2 days of symptom onset. The average incubation period reported by Weijie Guan *et al.* was 4 days (2 - 7 days) [24], while that reported by Li Qun *et al.* was 5.2 days (4.1 - 7.0 days) [26]. Fever and cough were the most common clinical symptoms in all the cases, with fever occurring in 73.4% and cough in 63.6% of the patients. Compared with other studies, our results were different. In the study by Guan Weijie *et al.* [24], 43.8% of the patients were found to have fever at the first visit, but the number increased to 88.7% after hospitalisation. In our study, of all the patients with fever,

more than half had mild to moderate fever (37.5˚C - 39˚C), and only a few had a high fever (23.1%).

The laboratory test results of both the groups were abnormal to different degrees, especially in patients with severe diseases. Blood glucose, serum sodium, serum albumin, amyloid A, and CRP values were found to be outside the normal range in both the groups. We suggested that the difference in laboratory results between the 2 groups can be used for assessing the degree of illness to some extent. Sijiao Wang *et al.* suggested that older age, hypertension, diabetes, and lymphopenia were risk factors for severity of COVID-19 [22], which was somewhat similar with the result of our study. In addition, the possible explanation was that SARS-CoV-2, a novel virus, greatly triggers the body's innate immune response, adaptive response, and specific immune response after entering the body through the respiratory tract [27]. The specific immune response depends primarily on T cells, and the critical protective role of T cell immune response to coronavirus infection has been well documented in several animal models [28]. The virus can trigger a terrible cytokine storm in the pulmonary tissue by releasing various types of mediators causing edema, air exchange dysfunction and acute respiratory distress syndrome (ARDS), acute cardiac injury followed by secondary infection which may lead to death [29] [30] [31].

In the early stage of the disease or in non-severe patients, the body's innate immune response and specific response can prevent the spread and clearance of the virus, similar to the immune response to other viruses invading the body. The response includes increased blood glucose level, accelerated CRP rates, increased amyloid A level, and other adaptive responses, as well as diluent serum albumin and blood sodium reduction. With the progress of the disease, despite the efforts of T cells, CD4, CD8 and other lymphocytes were reduced in severe patients or in the later stage of the disease owing to the virulence of the virus or the decline of the body's immunity. Qin *et al.* reported that increased neutrophil-to-lymphocyte ratio (NLR) as well as T lymphopenia, especially decreased number of CD4+ T cells, was typical in COVID-19 patients, particularly among the severe cases; however, no significant alteration in the CD8+ cells and B cells was reported [32]. Whether the mechanism is similar to that of HIV causing CD4 cell depletion remains to be investigated [33] [34]. At the same time, if the treatment is working well or if the patient's immune system recovers, the multiple organ dysfunction gets reversed. However, if the disease continues to progress or the treatment measures are not effective, multiple organs will fail, especially the lung, resulting in death. In Dawei Wang's study of 138 inpatients in Wuhan, the mortality rate was 4.3% [27], while the mortality rate was 1.4% in another study [24]. Accurate death rates require further statistics.

In all the cases in this study, only one 18-year-old patient presented no obvious imaging manifestations at the time of admission, and all the others showed imaging changes. Among the remaining 138 cases assessed using imaging changes, the lesions were more localized in the lung periphery (98%), and only a few severe patients showed inner or middle band lesions. This result was similar to

that in the Wenzhou case imaging study [35]. Possible explanation was that the blood supply of the subpleural was less than that of the intrapulmonary and mediastinum band, with a reduction in lymphatic reflux, resulting in a relatively low virus clearance capacity. There were more patchy heterogeneous density shadows in the severe patients. The possible explanation was that different exudate protein content would lead to different density on CT imaging, resulting in a variety of shapes and density changes. In 60% of all the patients, the lesions were distributed along the lung texture, suggesting that the spread along the bronchi may be one of the mechanisms for the spread of the virus. In addition, CT signs such as consolidation, bronchial inflation, and bronchiectasis were more common in the severe group; therefore, these signs could be used for assessing the severity of the disease.

In this study, age, body temperature, lymphocyte count, ADA value, blood oxygen partial pressure, IL-10, and bronchiectasis signs were selected by statistical methods for predicting the severity of COVID-19 patients, and the role of each variable in the prediction of severe COVID-19 was directly demonstrated in the form of the nomogram. Other studies have found predictors that are similar to us, such as age and lymphocyte count, and different from us, such as chronic history [20] [22] [36]. Clinicians can predict the severity of newly admitted patients according to their age, laboratory examination, and CT performance, and grasp the trend of the patient's condition for conducting more active treatments. This will greatly facilitate the clinical treatment of COVID-19 and benefit potential severe COVID-19 patients.

This study has some limitations. First, this study is a retrospective study and not a random study, which may affect the integrity of the data and reduce the credibility of the results. Second, this study only collected cases in Taizhou city. It would be better to collect a larger range of cases and analyse larger data. Third, there was no long-term follow-up in this study, which could not strongly reflect the specific benefits brought to the patients by predicting the development of the disease. In the future, we will work as far as possible with hospitals in other regions to share each other's data, expand the amount of data in our research, and continuously improve our predictive models. In addition, we will conduct long-term follow-up visits to the patients studied to see how the severity of COVID-19 affects the patient's physical condition and quality of life later in life. If we have the conditions, we will conduct joint prospective studies in areas where new cases are occurring to verify the validity and stability of our model.

5. Conclusion

In summary, our study analyzed the cases of patients with COVID-19 in Taizhou city and constructed a model to predict the illness severity which was of great significance for early identification and prompt treatment. When patients showed the features including older age, high body temperature, low lymphocyte count, low ADA value, low PaO_2, high IL-10, and bronchiectasis sign predict a greater likelihood of severe COVID-19.

Declarations

Ethics Approval and Consent to Participate

The retrospective multicentre cohort study was approved by the ethics review committee of Taizhou Hospital, Sanmen People's Hospital, Wenling First People's Hospital, and Tiantai People's Hospital, and the written informed consent was waived.

Consent for Publication

All authors agreed to publish the manuscript in the journal of International Journal of Clinical Medicine.

Availability of Data and Materials

All datasets are presented in the main paper.

Authors' Contributions

YK, SH and WJ designed the study and took the lead in drafting the manuscript and interpreting, SL and PP developed the statistical methods, SH, RZ, JW, RZZ, RL, HL, ZZ were participated in the collection of experimental data. All authors read and approved the final manuscript for publication.

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Conflicts of Interest

The authors declare that they have no competing interests.

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List of Abbreviations

CT: Computed tomography;
WHO: World Health Organization;
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2;
SARS-CoV: Severe acute respiratory syndrome coronavirus;
MERS-CoV: Middle east respiratory syndrome coronavirus;
PHEIC: Public Health Emergency of International Concern;
COVID-19: Coronavirus disease 2019;
CDC: Center for Disease Control and Prevention;
RT-PCR: reverse transcription polymerase chain reaction;
NGS: high throughput sequencing;
$PaCO_2$: Arterial blood oxygen partial pressure;
RR: Respiratory Rate;
FiO_2: oxygen concentration;
PH: potential of hydrogen;
C1q: Human Complement Component C1q;
IL-10: Interleukin-10;
TCD3: Total cluster of differentiation 3;
PT: Prothrombin time;
ADA: adenosine deaminase;
CK: Creatinine kinase;
LDH: Lactate dehydrogenase;
CRP: C-reactive protein;
HIV: Human immunodeficiency virus;
CD3/4/8: cluster of differentiation 3/4/8.

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Lymphocytopenia and Neutrophilia Deteriorate at the Lowest Oxygenation Index Timepoint in COVID-19 Patient

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Abstract

Objective: Coronavirus disease 2019 (COVID-19) spread throughout the world and caused hundreds of thousands of infected people to death. However, the pathogenesis of severe acute respiratory syndrome coronavirus-2 (SARS COV-2) is poorly understood. The objective of this study is to retrospectively explore the pathogenesis of COVID-19 from clinical laboratory findings, taking disease progression into account. **Methods:** A single-centered, retrospective study was carried out, which included moderate (n = 76) and severe COVID-19 cases (n = 22). The difference of laboratory findings from blood routine examination and hepatorenal function test were retrospectively evaluated between the state of moderate and severe. The disease progression was indicated by oxygenation index. **Results:** Age is a risk factor for disease progression from moderate to severe. Lymphocytopenia, neutrophilia, liver and kidney function decreasement occurred in severe patients on admission, compared with moderate patients. Lymphocytopenia and neutrophilia deteriorated at the lowest oxygenation index timepoint in the severe patients. And the oxygenation index was associated with ratio of lymphocyte and neutrophil in COVID-19 patients. **Conclusions:** Lymphocytopenia and neutrophilia, which deteriorate in the progression of severe patients, are the main pathogenesis of COVID-19. More measures need to be taken to control lymphocytopenia and neutrophilia in severe COVID-19. Oxygenation index presented potentiality

as predictor on the progression of COVID-19.

Keywords

COVID-19, Oxygenation Index, Lymphocytopenia, Neutrophilia, Glucocorticoids

1. Introduction

COVID-19 spreads throughout the world and has a mortality rate of about 7.1% [1]. As of December 9, 2020, the number of SARS-CoV-2 cases globally had eclipsed nineteen million, which largely exceeds the total number of SARS cases during the 2003 epidemic, and more than one million and five hundred thousand people have now died. The outbreak of COVID-19 has put health authorities on high alert in China and across the globe. Preliminary data indicates that COVID-19 can produce acute respiratory distress syndrome (ARDS), which is the leading cause of death. However up to now, the pathogenesis by which SARS-COV-2 triggers ARDS is poorly understood.

The aim of this study is to retrospectively explore the pathogenesis of COVID-19 from clinical laboratory findings, taking disease progression into account. The laboratory findings from our hospital were collected and a retrospective study of the differences in neutrophil, lymphocyte and so on during the moderate and most severe phases of COVID-19 was carried out. As a key lung function indicator, the oxygenation index was chosen as an indicator of the disease progression.

2. Materials and Methods

This study was approved by the ethics commission of Zhejiang Province Taizhou Hospital. All data were anonymized to comply with the provisions of personal data protection legislation. Due to the retrospective nature of this study and due the fact that only historical medical data were collected, written informed consent was not required.

2.1. Study Design and Participants

This single-center, retrospective study was carried out at Taizhou Hospital of Zhejiang province (Zhejiang, China). This hospital was specifically set up for the treatment of COVID-19 patients. We retrospectively recruited patients seen at the hospital between January 23, 2020 and February 27, 2020 and diagnosed with COVID-19 according to WHO's interim guidelines [2]. These participants had been treated and discharged from hospital. The patients were considered to have moderate disease if they displayed fever, respiratory tract symptoms, or imaging evidence of pneumonia. Patients were considered severe cases if their resting respiratory rate was >30 per minute, oxygen saturation was below 93% without oxy-

gen, or oxygenation index (PAO_2/FiO_2) or multiple pulmonary lobes showed >50% disease progression within 48 hours of imaging [3].

2.2. Data Collection

We reviewed clinical electronic medical records, nursing records, laboratory results, and radiological examinations for all patients with confirmed SARS-CoV-2 infection. Demographic data (age, sex, body weight), medical history, exposure history, underlying conditions, symptoms, laboratory results and treatment (respiratory support, antiviral therapy, corticosteroid therapy, immunoglobulin and vitamin C, etc.) were collected. Data were reviewed by a trained team of physicians.

2.3. Laboratory Confirmation

Sputum and throat swab specimens collected from all patients at admission were analyzed RT-qPCR for SARS-CoV-2 RNA within 3 hours of collection, using novel coronavirus (2019-nCoV) nucleic acid detection kit (Shanghai Zhijiang Biotechnology Co., China) by following the manufacturer's instructions. The primers used target SARS-CoV-2 RdRp, N and E genes. Samples were considered SARS-COV-2 positive if they were RdRp positive and positive for either the N or E gene. Where only the RdRp gene was positive, the test was repeated and the sample was considered SARS-COV-2 positive if both tests returned positive. Samples were considered SARS-COV-2 negative if they were negative for all 3 genes. Conditions for the amplifications were 45˚C for 10 min, 95˚C for 3 min, followed by 45 cycles of 95˚C for 15 s and 58˚C for 30 s.

2.4. Patients' Treatment

Patients were treated with the antiviral agents (lopinavir/Ritonavir oral solution or arbidol). Nebulized recombinant interferon α2b (rIFNα2b) was given at admission for about 10 days (5×10^6 IU, bid). Patients were randomly orally administered with vitamin C at a dose of 200 mg, 3 times daily. Low dose of corticosteroid (methylprednisolone, 12 - 50 mg daily for 5 - 7 days), and immunoglobulin (for 2 - 3 days) were administered in case of symptom deterioration. Nasal cannula oxygen support was given to patients depending on the severity of hypoxaemia. Patients with elevated inflammatory markers were treated with antibiotics (oral or intravenous). Patients with hepatic insufficiency indicated by Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) were given reduced glutathione, compound ammonium glycyrrhizinate, diaminonium glycyrrhizate or bicyclol. Renal insufficient patients were treated with reduced glutathione or compound α-ketoacid. To monitor viral clearance, SARS-CoV-2 tests were done at least twice before hospital discharge.

2.5. Statistical Analysis

Continuous variables were expressed as median (IQR) and compared using stu-

dent's t test if data were normally distributed or otherwise, Mann-Whitney U test. Categorical variables were expressed as proportions (%) and compared by χ^2 test or Fisher's exact test when the data was limited between moderate and severe patients, or between the most severe timepoint and hospital discharge. Pearson correlation analysis was conducted to assess the association of oxygenation index with lymphocytopenia and neutrophilia. Linear regression was conducted to explore which factor is responsible for lowered oxygenation index. Tests were two-sided with significance set at $\alpha \leq 0.05$. Data analysis was done on SPSS software, version 16.0 (SPSS Inc).

3. Results

3.1. Demographics and Baseline Characteristics of Patients with Severe COVID-19

98 hospitalized patients, laboratory confirmed to be SARS-COV-2 positive, were included in the study. The average age for the participants was 45.8 years (Std. Error (SE), 1.4). Of these, 58 (59.2%) were male. 76 (78.6%) of the participants were considered to be moderate cases, while 22 (22.4%) were considered to be severe cases (Table 1). The median duration from symptom onset to hospital admission, hospital length of stay (HLOS) and clinic course were 6 days (IQR, 5), 15.6 days (IQR, 11), and 21.7 days (IQR, 9), respectively. Of the 98 patients, 32 (32.7%) had 1 or more comorbidities. Hypertension [13 (13.3%)], diabetes [6 (6.1%)], cancer [4 (4.1%)], and chronic liver disease [3 (3.1%)] were the most common underlying conditions (Table 1).

Table 1. Demographics and baseline characteristics of patients with COVID-19.

	Total (n = 98)	Moderate cases (n = 76)	Severe cases (n = 22)	P Value
Age, mean ± Std.Error, y	45.8 ± 1.4	43.1 ± 1.5	55.1 ± 2.2	0.000
Sex				
Male, n (%)	58 (59.2)	45 (60)	12 (54.5)	0.65
Body weight, median (IQR), kg	65 (16.5)	65 (15.5)	70 (17.0)	0.13
Comorbidities				
Hypertension, n (%)	13 (13.3)	7 (9.2)	6 (27.3)	0.065
Diabetes, n (%)	6 (6.1)	3 (3.9)	3 (13.6)	0.24
Malignancy, n (%)	4 (4.1)	3 (3.9)	1 (4.5)	1.000
Chronic liver disease, n (%)	3 (3.1)	3 (3.9)	0 (0)	1.0
Chronic kidney disease, n (%)	2 (2.0)	1 (1.3)	1 (4.5)	0.40
Hypothyroidism, n (%)	1 (1.0)	1 (1.3)	0 (0)	1.0
Syphilis, n (%)	1 (1.0)	0 (0)	1 (4.5)	0.22
Chronic bronchitis, n (%)	1 (1.0)	1 (1.3)	0 (0)	1.0
Gout, n (%)	1 (1.0)	0 (0)	1 (4.5)	0.22
Pregnancy, n (%)	1 (1.0)	1 (1.3)	0 (0)	1.0

Continued

Drug therapy				
Antiviral agents, n (%)	98 (100)	76 (100)	22 (100)	1.0
rIFNα2b, n (%)	98 (100)	76 (100)	22 (100)	1.0
Glucocorticoids, n (%)	21 (21.4)	4 (5.3)	17 (77.3)	0.000
Immunoglobulin, n (%)	16 (16.3)	2 (2.6)	14 (63.6)	0.000
Vitamin C, n (%)	24 (24.5)	17 (22.4)	7 (31.2)	0.36
Antibacterial agents, n (%)	32 (32.7)	20 (26.3)	12 (54.5)	0.013
Onset of symptom to Hospital admission, median (IQR), d	6.0 (5.0)	5.0 (5.0)	6.5 (7.8)	0.40
HLOS, median (IQR), d	15.6 (11.0)	13.0 (11.0)	20.5 (8.5)	0.001
Clinic course, median (IQR), d	21.7 (9)	19.5 (8.8)	26.5 (14.3)	0.000

P values comparing moderate cases and severe cases are from χ^2 test, Fisher's exact test, Mann-Whitney U test or Student's t test. IQR, interquartile range.

Compared with moderate cases, the severe patients were significantly older [average age, 55.1 years (SE, 2.2) vs 43.1 years (SE, 1.5), P < 0.001]. Relative to moderate cases, severe cases were associated with longer HLOS and clinic course [median, 20.5 days (IQR, 8.5) vs 13 days (IQR, 11.0), P = 0.001; 26.5 days (IQR, 14.3) vs 19.5 days (IQR, 8.8), P < 0.001, respectively]. Relative to moderate cases, significantly more severe patients were treated with antibacterial agents, glucocorticoids and immunoglobulin [12 (54.5%) vs 20 (26.3%), P = 0.013; 17 (77.3%) vs 4 (5.3%), P < 0.001; 14 (63.6%) vs 2 (2.6%), P < 0.001, respectively]. There were no differences in the percentage of vitamin C therapy given to moderate and severe cases [7 (31.2%) vs 17 (22.4%)] (Table 1).

3.2. Deterioration of Lymphocytopenia and Neutrophilia at the Lowest Oxygenation Index Timepoint

COVID-19 symptoms continued to progress after hospital admission. During hospital stay, the patients underwent multiple oxygenation index assays, a key lung function indicator. The lowest oxygenation index was chosen as the most severe timepoint. The laboratory results for tests done at admission, at the most severe timepoint and before discharge were analyzed. This analysis revealed that laboratory results for moderate cases remain relatively stable between the admission and the lowest oxygenation timepoint. At admission, the lymphocyte ratio in severe cases was significantly lower than in moderate cases [median, 23.6 (IQR, 20.85) vs 25.75 (IQR, 9.8), P = 0.041], while the neutrophil ratio was higher in severe cases [median, 66.1 (IQR, 27.25) vs 65 (IQR, 14.43), P = 0.039]. At the most severe timepoint, the lymphocyte ratio in severe cases decreased sharply, and was lower than the lymphocyte ratio in moderate cases [median, 11.55 (IQR, 15.58) vs 25.5(IQR, 13.95), P < 0.001]. Neutrophil ratio and white-cell counts were significantly higher than in moderate cases [median, 81.25 (IQR, 21.8) vs 66.1 (IQR, 16.12), P < 0.001; 8.05 (IQR, 4.93) vs 6.0 (IQR, 2.05), P = 0.006, respectively] (Table 2).

Table 2. Laboratory results of patients infected with SARS CoV-2.

	On admission	At the lowest oxygenation index time				Discharge from hospital			
	Moderate case	Severe case	P Value	Moderate case	Severe case	P Value	Moderate case	Severe case	P Value[a]	P Value[b]
Oxygenation index (mmHg)	452 (105)	329 (149.5)	0.000	452 (121.75)	234 (72)	0.000	481.5 (273)	374 (98.5)	0.002	0.000
Lactate (mmol/L)	1.75 (0.85)	1.9 (0.9)	0.88	1.7 (0.68)	1.95 (1.32)	0.040	1.7 (1.07)	1.7 (1.22)	0.388	0.54
White-cell count ($\times 10^9$/L)	5.3 (2.05)	5.5 (3.75)	0.79	6.0 (2.05)	8.05 (4.93)	0.006	6.0 (1.7)	6.95 (3.83)	0.000	0.21
Lymphocyte ratio (%)	25.75 (9.8)	23.6 (20.85)	0.041	25.5 (13.95)	11.55 (15.58)	0.000	25.3 (9.03)	19.9 (15.75)	0.459	0.000
Neutrophil ratio (%)	65 (14.43)	66.1 (27.25)	0.039	66.1 (16.12)	81.25 (21.8)	0.000	62.85 (11.9)	66.3 (15.38)	0.002	0.000
Platelet count ($\times 10^9$/L)	209 (62.5)	185 (128.5)	0.23	217.5 (73.25)	230.5 (111.25)	0.57	270 (100.5)	205.5 (100.25)	0.003	0.001
Alanine aminotransferase (U/liter)	18 (17.75)	30 (24)	0.032	18 (17)	28 (20.25)	0.005	20.5 (22.5)	26.5 (15.5)	0.136	0.27
Aspartate aminotransferase (U/liter)	22 (8.0)	31 (23.5)	0.001	24 (8.5)	23.5 (16.0)	0.29	21.0 (7)	22.0 (6)	0.989	0.053
Total bilirubin (μmol/L)	13.15 (9.42)	15.3 (13.55)	0.51	14.4 (7.18)	16.1 (15.4)	0.95	12.7 (4.78)	11.8 (7.55)	0.122	0.28
Direct bilirubin (μmol/L)	4.85 (3.38)	6.2 (5.6)	0.25	5.35 (2.45)	6.25 (6.10)	0.68	3.95 (1.5)	3.0 (2.6)	0.024	0.001
Indirect bilirubin (μmol/L)	8.15 (5.85)	9.1 (7.6)	0.67	9.0 (5.5)	10.20 (7.78)	0.90	8.7 (3.93)	8.15 (5.02)	0.239	0.91
Uric acid (μmol/L)	266 (128.75)	252 (170.5)	0.23	257 (139.5)	224 (128)	0.028	273 (116)	269.5 (95.25)	0.040	0.29
Creatinine (μmol/L)	77 (22)	73 (21)	0.77	78 (20)	73 (23.75)	0.38	76.5 (21.25)	69 (17.5)	0.242	0.036
Blood urea nitrogen (mmol/L)	4.18 (1.7)	4.19 (1.74)	0.55	3.84 (1.23)	5.03 (3.6)	0.044	3.41 (1.72)	3.78 (1.7)	0.023	0.53
Creatinine clearance rate (ml/min)	101.5 (22)	86 (19.5)	0.003	102 (15.75)	86 (18)	0.021	103.5 (28.75)	92 (18.5)	0.135	0.52

Data are showed as median (IQR).[a]P values comparing moderate cases and severe patients from Mann-Whitney U test. [b]P value comparing the lowest oxygenation index timepoint and discharge from hospital of all the patients.

At hospital discharge, oxygenation index, lymphocytopenia and neutrophilia were significantly improved after multiple rounds of treatment ($P < 0.001$), when compared to the most severe timepoint. However, neutrophil ratio and white-cell counts in severe cases remained higher than in moderate cases [median, 66.3 (IQR, 15.38) vs 62.85 (IQR, 11.9), $P = 0.002$; 6.0 (IQR, 1.7) vs 6.95 (IQR, 3.83), $P < 0.001$, respectively]. Notably, the platelet count in severe cases was significantly lower than in moderate cases [median, 205.5 (IQR, 100.25) vs 270 (IQR, 100.5), $P = 0.003$] (Table 2).

Liver and kidney functions were monitored by analyzing alanine and aspartate aminotransferase levels, as well as creatinine clearance rate. This analysis revealed that liver and kidney function in the severe cases were poorest at admission but improved gradually. Relative to the moderate cases, lower levels of uric acid, an endogenous free radical scavenger and a major antioxidant in plasma [4], were observed in severe cases at the lowest oxygenation index timepoint [median, 224 (IQR, 128) vs 257 (IQR, 139.5), $P = 0.028$] (Table 2). However, li-

near regression analysis suggests that the lower uric acid levels might be age and sex related and not oxygenation index dependent (uric acid = 468.65 − 1.721 age − 56.244 sex − 0.07 oxygenation index, Adjusted R Square = 0.098, P = 0.036, 0.009, 0.295 for age, sex, oxygenation index, respectively).

3.3. Association of Oxygenation Index with Lymphocytopenia and Neutrophilia

To evaluate the relationship of oxygenation index with lymphocytopenia and neutrophilia, the Pearson correlation analysis and linear regression analysis were carried out. The association of oxygenation index with lymphocytopenia and neutrophilia were demonstrated by Pearson correlation analysis of the values at the most severe timepoint (r = 0.465 with neutrophil ratio, P < 0.001; r = −0.461 with lymphocyte ratio, P < 0.001) (Figure 1). Linear regression analysis showed that age and liver function were the factors that influenced the oxygenation index levels (oxygenation index = 790.777 − 39.816 age − 2.799 sex − 1.627 body weight − 2.385 ALT + 0.536 AST − 0.404 creatinine clearance rate − 2.672 comorbidities, Adjusted R Square = 0.141, P = 0.006, 0.043, 0.226, 0.299, 0.739, 0.563, 0.912 for age, ALT, sex, body weight, AST, creatinine clearance rate, comorbidities, respectively). Syphilis, gout, hypothyroidism were not included in comorbidities here as neither of them was reported to be related with the risk of COVID-19 in the literature.

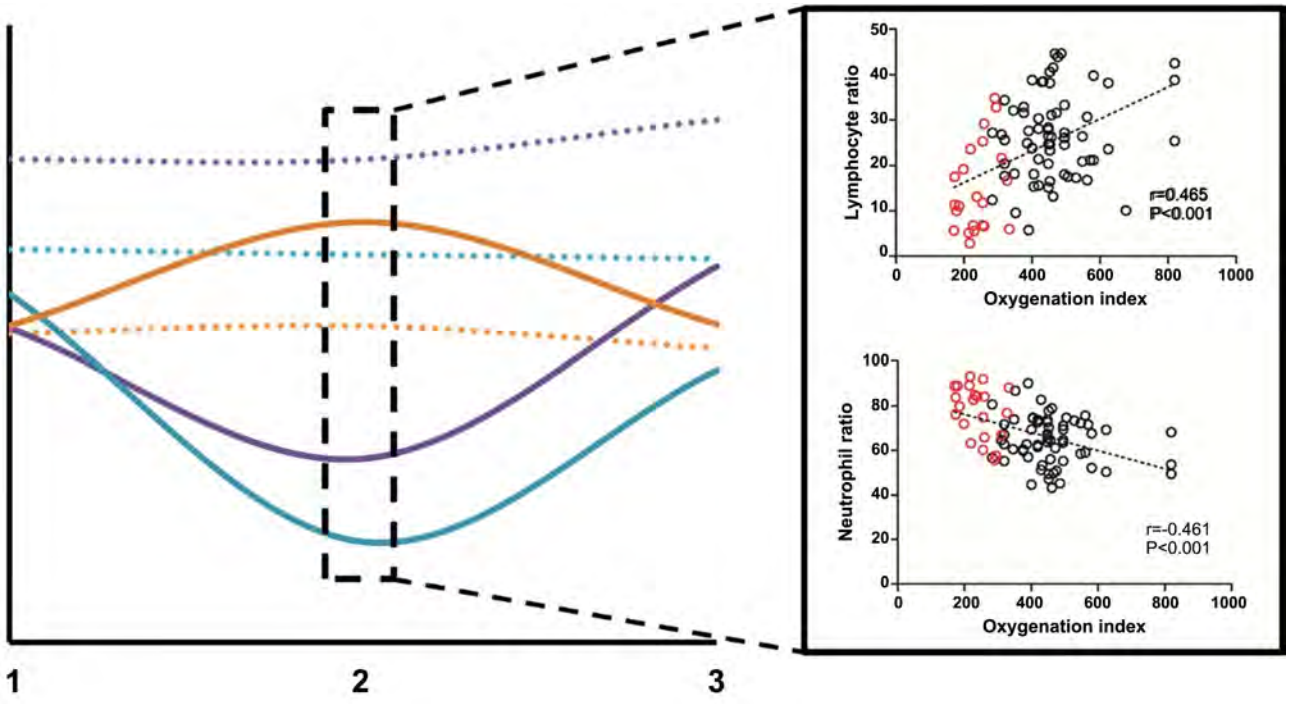

Figure 1. Association of oxygenation index with lymphocyte ratio and neutrophil ratio in COVID-19 patient. Left is changes of oxygenation index (purple), lymphocyte ratio (blue) and neutrophil ratio (orange) in moderate cases (dotted line) and severe cases (solid line). 1, On admission; 2, Lowest oxygenation index timepoint; 3, Discharge from hospital. Right is results of Pearson correlation analysis of oxygenation index with lymphocyte ratio (upper) and neutrophil ratio (lower). Black circles, moderate cases; red circles, severe cases. r = Pearson's coefficient; P, significance.

4. Discussion

COVID-19, which spread rapidly and has been considered as a global pandemic, has a fatality rate of about 7.1% fatality [1]. However, its pathogenesis is poorly understood. We have successfully treated 98 SARS-CoV-2 positive patients displaying moderate or severe symptoms and all have been discharged from hospital. Findings from the retrospective analysis of these patient's primary clinical data can help to better understand the COVID-19 pathogenesis. Because dyspnea and subsequent ARDS [5] [6] is the main complication from COVID-19, we chose the lowest oxygenation index as the most severe COVID-19 timepoint. We observed that lymphocytopenia and neutrophilia were the main features of the disease at the most severe timepoint and COVID-19 progression is accompanied by a deteriorating lymphocytopenia and neutrophilia. Several other studies have also shown that lymphocytopenia and neutrophilia were the clinical characteristics in critical patient or nonsurvivors, compared to the noncritical or survivors [6] [7] [8] [9]. Nevertheless, this is the first study takes disease progression into account indicating by the oxygenation index.

Oxygenation index was shown to be related with lymphocytopenia and neutrophilia after Pearson correlation analysis in this study and also with radiographic score in [10]. Oxygenation index presented potentiality as predictor on the progression of COVID-19. Because of small sample size and lack of image data, the criterion of oxygenation index for COVID-19 deterioration was not achieved. Some COVID-19 patients with "silent hypoxemia" deteriorate rapidly without signs of respiratory distress [11]. Moreover, oxygenation index is easy to calculate and suitable for clinical application in admission units during a pandemic. It is recommended to routinely monitor the oxygenation index and increase oxygen delivery once it decreases. As age and ALT influenced the oxygenation index levels shown in linear regression analysis, it is needed to pay attention to the liver function in elderly patients [12].

Our data implies four means of COVID-19 pathogenesis: 1) Like SARS-CoV [13], SARS-CoV-2 invades and destroys lymphocytes [14]. 2) Neutrophils, as part of the innate immune system, increase sharply to help clear exogenous virus. At the same time, high levels of reactive oxygen species are produced, which may cause injury to the lung epithelial-endothelial barrier [15]. 3) A cytokine storm triggered by the destroyed lymphocytes and hyperactive neutrophils might occur in severe COVID-19 [16] [17]. 4) An overactive immune response causes diffuse alveolar damage, airway inflammation and increased secretions overflowed from the alveoli, leading to the airways blockage and dyspnea [18] [19]. A subset of patients specially with comorbidities such as hypertension or diabetes develop acute respiratory distress syndrome (ARDS), multiple organ failure and/or septic shock, which are high risk indication of death.

Interventions that manage these COVID-19 consequences should be beneficial in clinic practice. Clinical applications such as thymosin and gamma globulin will improve the COVID-19 patients' poor immune function [20]. Therapeu-

tic strategies targeting neutrophilia by reducing neutrophil numbers, blocking neutrophil activation or blocking neutrophil-derived mediators will provide new options for clinical SARS-CoV-2-induced pneumonia [21]. Treatment options for patients with severe inflammation include steroids, intravenous immunoglobulin, selective cytokine blockers (such as anakinra or tocilizumab [22] [23]) and JAK inhibitors. A multicenter randomized controlled trial of tocilizumab (IL-6 receptor blocker) has been approved for clinical trials in patients with covid-19 pneumonia and elevated IL-6 in China (ChiCTR2000029765).

In our hospital, various measures were taken to treat COVID-19 patients and their benefits in inhibition of lymphocytopenia and neutrophilia and subsequent inflammatory storm deserve to be discussed. Interferon interferes with virus replication and transmission through mechanisms such as reducing cell metabolism or cytokine secretion which could promote the activation of adaptive immunity and it may upscale treatment in early stages of COVID-19 infection [24]. The results that SARS-CoV-2 failed to induce IFNs expression supports that exogenous IFN treatment might be beneficial for COVID-19 [25]. On the other hand, interferon stimulates gene expression of ACE2, SARS-CoV-2 receptor, in human airway epithelial cells. Whether interferon is net beneficial or detrimental in COVID-19 needs studied [26].

Glucocorticoid is a widely used and effective anti-inflammatory and immunosuppressive agent. Low dose of glucocorticoids was used for a few days here, which was not associated with severe sequelae, when the oxygenation index fell sharply. This treatment could be critical in reversing COVID-19 complications [27] [28]. Deteriorating severe patients also received immunoglobulin which could neutralize the pathogens, block the receptors on virus-targeted cells and inhibit production of inflammatory factors. Immunoglobulin was reported to reduce HLOS and 28-day mortality of patients with severe COVID-19 pneumonia [29]. In lymphocytopenia situation, patients were seldom treated with thymosin. However, thymosin was reported to reverses T cell exhaustion in a retrospective study [20]. Vitamin C is supposed to alleviate COVID-19 symptoms by scavenging reactive oxygen and nitrogen species and also modulation of the immune system. However, any impact of vitamin C administration on lymphocytopenia, neutrophilia, HLOS or clinic course of the disease was not observed, upon analysis of differences of laboratory findings between the treated and untreated group (**Supplementary Table S1**) and regression of vitamin C to changes of laboratory results. This may be due to the short metabolic half-life and low dose of vitamin C used [30].

Considering the information described above, the deteriorating lymphocytopenia and neutrophilia was observed in the progression of severe COVID-19 patients. Oxygenation index presented potentiality as predictor on the progression of COVID-19. These findings indicate that the oxygenation index should be routinely monitored and measures need to be taken to control lymphocytopenia, neutrophilia and the resulting cytokine storm. Symptomatic treatments such as low dose of glucocorticoids and immunoglobulin possess possible benefit on

COVID-19 amelioration.

This study has several limitations. First, the sample size is small. Only 22 severe patients were included. Second, image data were not collected. Because of the two shortcomings, the causal relationship and criterion of decreasement of oxygenation index for COVID-19 deterioration was not achieved. Third shortcoming comes from the retrospective observational nature of this study, so it is difficult to address the relationships between COVID-19 amelioration and symptomatic therapy such as glucocorticoids and vitamin C.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary

Table S1. The effect of oral vitamin C administration on the patients with COVID-19.

	On admission			Discharge from hospital		
	Vc (n = 24)	no Vc (n = 74)	P value	Vc (n = 24)	no Vc (n = 74)	P value
Oxygenation index (mmHg)	424 (165.0)	443 (118.5)	0.63	471 (132)	410 (224)	0.46
Lactate (mmol/L)	1.75 (0.78)	1.8 (0.95)	0.78	1.6 (1.35)	1.8 (1.1)	0.94
White-cell count ($\times 10^9$/L)	5.4 (2.4)	5.4 (2.15)	0.85	5.9 (2.55)	5.7 (3.2)	0.73
Lymphocyte count ($\times 10^9$/L)	66.8 (12.93)	65.4 (16.4)	0.58	26.4 (9.35)	22.9 (10.6)	0.76
Neutrophil count ($\times 10^9$/L)	24.65 (11.4)	25.9 (13.35)	0.65	62.4 (10.75)	64.6 (51.6)	0.97
Platelet count ($\times 10^9$/L)	213 (97.5)	204 (67)	0.96	245 (105)	258 (148)	1.0
Alanine aminotransferase (U/liter)	17 (14.75)	21 (20.5)	0.18	20 (14.5)	26 (17.0)	0.10
Aspartate aminotransferase (U/liter)	20.5 (7.75)	24 (11.0)	0.11	19 (6.5)	22 (7.0)	0.081
Total bilirubin (μmol/L)	14.05 (11.13)	13.1 (9.25)	0.87	13.4 (6.7)	12.2 (5.7)	0.63
Direct bilirubin (μmol/L)	5.2 (3.45)	4.8 (3.7)	0.96	3.9 (1.75)	3.8 (2.0)	0.96
Indirect bilirubin (μmol/L)	8.5 (7.58)	8.2 (5.4)	0.86	9.7 (5.2)	8.5 (4.2)	0.57
Uric acid (μmol/L)	252 (94)	266 (152.5)	0.47	282 (85)	267 (116)	0.86
Creatinine (μmol/L)	75.5 (25.75)	76 (21)	0.90	76 (16.5)	74 (20)	0.92
Blood urea nitrogen (mmol/L)	3.96 (1.58)	4.19 (1.82)	0.87	3.69 (1.69)	3.6 (1.83)	0.77
Creatinine clearance rate (ml/min)	103 (23.25)	95 (23.5)	0.32	101 (23.5)	95 (27)	0.42
HLOS (d)				12 (12.5)	16 (11)	0.28
Clinic course (d)				19 (12.5)	21 (9)	0.92

Data are showed as median (IQR). P values comparing with vitamin C (Vc) or no vitamin C (no Vc) treatment are from Mann-Whitney U test.

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- Clinical Endocrinology and Metabolism
- Clinical Epidemiology
- Clinical Forensic Medicine
- Clinical Gastroenterology and Hepatology
- Clinical Genetics
- Clinical Haematology
- Clinical Hypertension
- Clinical Imaging
- Clinical Immunology
- Clinical Implant Dentistry and Related Research
- Clinical Interventions in Aging
- Clinical Laboratory Analysis
- Clinical Linguistics & Phonetics
- Clinical Lipidology
- Clinical Microbiology and Antimicrobials
- Clinical Microbiology and Infection
- Clinical Microbiology and Infectious Diseases
- Clinical Molecular Pathology
- Clinical Monitoring and Computing
- Clinical Neurology and Neurosurgery
- Clinical Neurophysiology
- Clinical Neuropsychology
- Clinical Neuroradiology
- Clinical Neuroscience
- Clinical Nursing
- Clinical Nutrition
- Clinical Obstetrics and Gynaecology
- Clinical Oncology and Cancer Research
- Clinical Ophthalmology
- Clinical Oral Implants Research
- Clinical Oral Investigations
- Clinical Orthopaedics and Related Research
- Clinical Otolaryngology
- Clinical Pathology
- Clinical Pediatric Emergency Medicine
- Clinical Periodontology
- Clinical Pharmacology & Toxicology
- Clinical Pharmacy and Therapeutics
- Clinical Physiology and Functional Imaging
- Clinical Practice and Epidemiology in Mental Health
- Clinical Psychology and Psychotherapy
- Clinical Psychology in Medical Settings
- Clinical Radiology
- Clinical Rehabilitation
- Clinical Research and Regulatory Affairs
- Clinical Research in Cardiology
- Clinical Respiratory
- Clinical Rheumatology
- Clinical Simulation in Nursing
- Clinical Sleep Medicine
- Clinical Techniques in Small Animal Practice
- Clinical Therapeutics
- Clinical Toxicology
- Clinical Transplantation
- Clinical Trials
- Clinical Ultrasound
- Clinical Virology
- Complementary Therapies in Clinical Practice
- Consulting and Clinical Psychology
- Contemporary Clinical Trials
- Controlled Clinical Trials
- Diabetes Research and Clinical Practice
- Evaluation in Clinical Practice
- Fundamental & Clinical Pharmacology
- Hereditary Cancer in Clinical Practice
- Human Psychopharmacology: Clinical and Experimental
- Innovations in Clinical Neuroscience
- Laboratory and Clinical Medicine
- Neurophysiologie Clinique/Clinical Neurophysiology
- Nutrition in Clinical Practice
- Pacing and Clinical Electrophysiology
- Psychiatry in Clinical Practice
- Therapeutics and Clinical Risk Management
- Veterinary Clinical Pathology

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