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The systemic capillary leak syndrome following COVID-19 vaccine

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ABSTRACT

The COVID-19 outbreak has been declared the sixth Public Health Emergency of International Concern certified by the World Health Organization. With the extensive application of COVID-19 vaccines, rare but serious adverse reactions have gradually emerged, among which systemic capillary leak syndrome (SCLS) deserves our attention. SCLS is difficult to diagnose. Not only can it exacerbate various diseases, but also can lead to pulmonary edema, kidney failure, and even death. We summarized and discussed case reports of SCLS induced by COVID-19 vaccines to raise awareness of COVID-19 vaccine-associated rare diseases. We conducted a comprehensive search in Web of Science, PubMed and Embase and collected case reports of SCLS induced by COVID-19 vaccine before February 19, 2024. We identified and analyzed 12 articles, encompassing 15 cases. We synthesized the data to summerize possible mechanisms of SCLS, clinical manifestations, differential diagnoses, and therapeutic approaches. Most SCLS occurred after vaccination with the Pfe-Biontech mRNA vaccine (9/15) and following the second vaccination (10/15). Almost all patients experienced hypotension (13/15) and tachycardia (11/15). Most patients received intravenous fluids (9/15) and corticosteroids (9/15). 11 patients were recovered and were discharged, while 4 patients died. Inflammation and endothelial cell damage may be linked to SCLS and COVID-19 vaccines. These findings highlight the necessity of focusing on serious adverse reactions of COVID-19 vaccines and the urgency to reconsider the safety of COVID-19 vaccines.

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KEYWORDS
COVID-19; vaccines; systemic capillary leak syndrome; adverse reaction; mechanism

Introduction

The COVID-19 pandemic, which erupted globally in 2019, has become one of the most significant health crises of this century. Since the outbreak of the COVID-19 pneumonia in 2020, vaccines have been developed and have proven to be highly effective in preventing and treating the disease.[1,2] The COVID-19 vaccines are mainly classified into four types based on the development process, including the mRNA vaccine (BNT162b2), the non-replicating adenovirus vector-based DNA vaccines (AZD1222/ChAdOx1), the inactivated virus vaccine (CoronaVac) and subunit vaccines.[3,4] Although the safety and efficacy of these vaccines in preventing and treating COVID-19 pneumonia have been demonstrated, a certain number of patients have experienced adverse reactions post-vaccination, including capillary leak syndrome and anaphylaxis.[5]

The systemic capillary leak syndrome (SCLS) refers to a disease characterized by increased permeability of capillaries to proteins, causing protein-rich fluid to flow from inside the blood vessels to the tissue space,[6,7] which has been categorized several types, including idiopathic(Clarkson), drug-induced and others. The specific and definitive treatment guidelines for the various subtypes remain to be further defined. The prominent features of SCLS are hypotension, hemoconcentration and hypoalbuminemia.[8] SCLS can be triggered by a variety of disorders. When capillary leak syndrome occurs in the context of hematologic malignancy treatment and the shared pathophysiology of these disorders is to cause a surge in systemic cytokine storms, resulting in capillary endothelial cell injury on the cellular level,[9] thereby increasing capillary permeability and leading to the exudation of intravascular material. The role of mediators other than cytokines is not well known. Several studies and case reports have indicated the possible relationship between COVID-19 vaccination and SCLS.[5,10–12]

Although the causal relationship and specific mechanism between COVID-19 vaccination and the pathogenesis of SCLS have not been fully elucidated, the occurrence of rare adverse reactions post-vaccination has garnered significant clinical attention. This study summarizes the case reports of SCLS after COVID-19 vaccination, summarizes its basic information, clinical manifestations, vaccination status, etc., and analyzes the possible mechanisms, which provides a direction for future related research and helps to improve clinicians' awareness of this rare side effect.

Methods

Search strategy

We consulted authoritative medical databases, including Web of Science, PubMed and Embase, to extensively collect and include case reports of SCLS diagnosed after COVID-19

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vaccination worldwide. We meticulously examined the relevant case reports from the beginning until January 30, 2024, and continued to follow up and study them in depth.On February 19, 2024, we conducted a second study to ensure the articles were thoroughly accurate.In addition, we researched all references in the included case reports to prevent any omissions. The search formula used in PubMed is as follows:((covid[Title/Abstract] OR cov[Title/Abstract] OR coronavirus[Title/Abstract]) AND (vaccine[Title/Abstract] OR vaccination[Title/Abstract] OR vaccinum[Title/Abstract])) AND (capillary leak syndrome[Title/Abstract] OR capillary leak[Title/Abstract] OR CLS[Title/Abstract]).We also employed similar methods and combinations of keywords in Web of Science and Embase to ensure the accuracy of our search. Additionally, we screened and excluded reviews, duplicate articles, experimental studies, observational studies and case reports with incomplete clinical information.

Data extraction

Firstly, we respectively retrieved 43, 21 and 31 relevant articles in Web of Science, PubMed and Embase databases using the above keywords and search formulas. Secondly, we filtrated duplicate articles ($n = 40$) from different databases. After removing these duplicate articles, we obtained 55 research articles, which were included in the scope of case screening. Finally, through careful browsing of these 55 articles, we selected 12 eligible articles, including 15 cases, which reported capillary leak syndrome within a certain period after COVID-19 vaccination, which is presented in Figure 1.

We systematically extracted and integrated the first author of each article as a representative to summarize the useful information of each study. We collected information about patients by category. The basic information includes the patient ‘s age, gender and region. Clinical features include the year of onset, past medical history, and clinical presentation. In addition, we also collected information related to vaccines, including the vaccine type, the vaccination times, time of onset after vaccination as well as data on treatment, outcome(recovery or died), and course of disease. These data have been compiled in Table 1. At the same time, we also summarized the highly relevant laboratory data and presented them in Table 2.

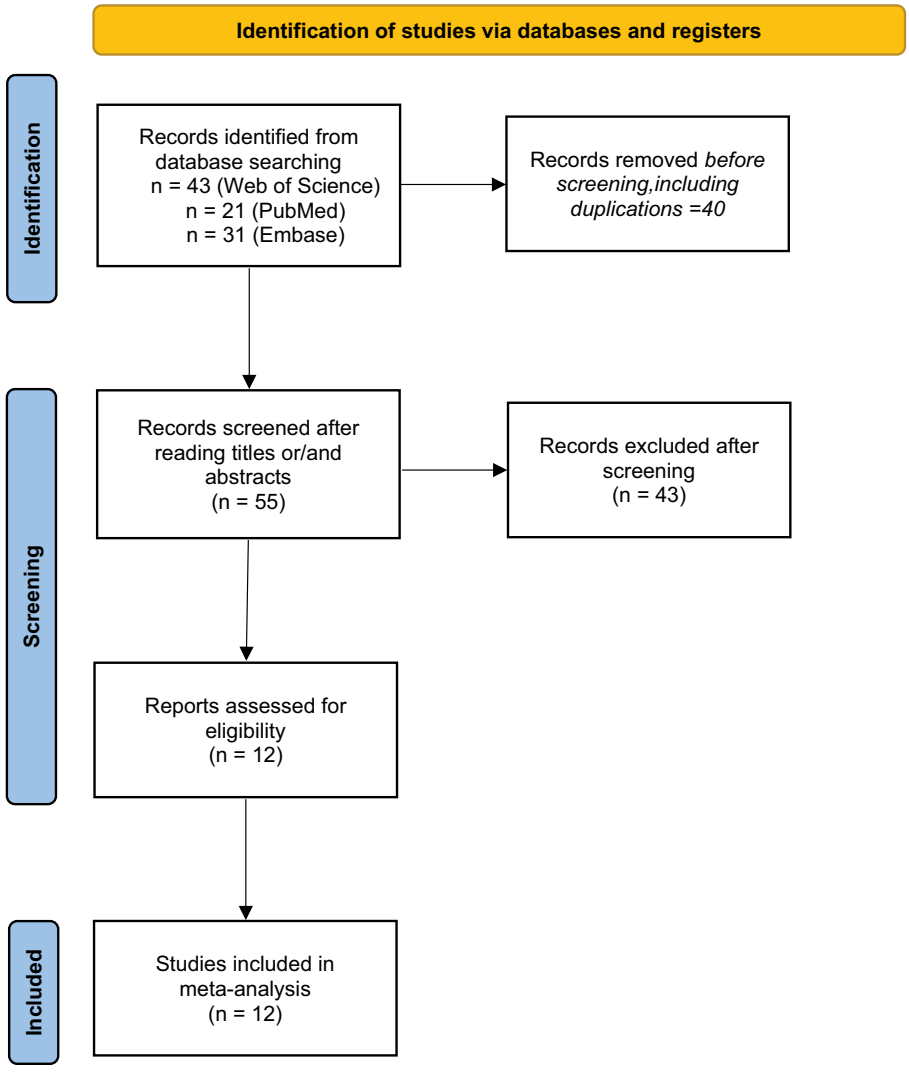

Figure 1. PRISMA flow diagram for study selection.

Table 1. Basic information of the 15 patients from case reports.

Reference	Year/ Region	Age/ Gender	Past medical history	MGUS	Vaccine type/times	Time of onset after vaccination	Clinical presentation	Treatment	Outcome	Course of disease
Buj M et al.[13]	2021/ Spain	38/M	None	IgG κ IgA κ	Pfizer-BioNTech mRNA vaccine /2nd	6 days	Intense pain in both lower limbs, general malaise, arthromyalgia, diarrhea, some isolated episodes of fever, hypotension and tachycardia	2 L of crystalloid solution, vasopressors,invasive mechanical ventilation and continuous renal replacement therapy	Recovery	9 days
Matheny M et al.[14]	2021/ USA	68/F	SCLS and monoclonal gammopathy, without intravenous immunoglobulin treatment	MGUS （2006）	Johnson & Johnson, Janssen /1st	2 days	Nausea, vomiting, syncope, hypotension and tachycardia	intravenous fluids, vasopressors, antibiotics, stress-dose corticosteroids, renal replacement, intravenous immunoglobulin (1 g/kg of body weight), and bilateral lower-ex tremity fasciotomies	Died	7 days
		46/F	Hypotension and edema attributed to amniotic fluid embolism, hypotension and asthma attributed to sepsis	IgG κ	Moderna COVID-19 vaccine /2nd	2 days	Influenza-like symptoms, hypotension, tachycardia, anasarca	intravenous fluids (Included 7 L of crystalloid and albumin boluses) vasopressors, antibiotics, and stress-dose corticosteroids	Recovery	7 days
		36/M	Syncope and seizure	None	Pfizer-BioNTech mRNA vaccine /2nd	1 days	Syncope, hypotension and tachycardia; Status epilepticus, cardiac arrest, anasarca, pulmonary edema, and pleural effusions	intravenous fluids, anticonvulsants, 4 vasopressors, antibiotics, and stress-dose corticosteroids	Recovery	10 days
Robichaud J et al.[8]	2021/ Canada	66/M	Monoclonal gammopathy and cardiac arrest	IgG κ （2017）	Oxford-AstraZeneca AZD1222 COVID-19 vaccine /1st	1 days	Generalized malaise, nausea, abdominal pain and dizziness, hypotension (93/ 60 mm Hg) with heart rate at 125 b.p.m, polycythemia (hemoglobin 223 g/L)	intravenous fluids, piperacillin – tazobactam and more than 6 L of fluid	Recovery	4 days
Yang C et al.[15]	2023/ Canada	50/F	Bilateral lower extremity swelling in 7 days and shortness of breathon exertion (NYHA class III severity) in 2 days	IgG κ	Oxford-AstraZeneca AZD1222 COVID-19 vaccine /not mention	5 weeks	Dyspnoea and chest pain, with non-pitting edema. Day 2, acute worsening of hypoxemia, hypotension, paresthesia and peripheral mottling with slow capillary refill.	A 1 g/kg of intravenous immunoglobulin, 7 L of crystalloids and 150 g of albumin and 150 g of albumin during the resolution phase	Recovery	15 days
Yatsuzuka K et al.[16]	2021/ Japan	65/M	Hypertension and generalized pustular psoriasis	None	Pfizer-BioNTech mRNA vaccine /2nd	2 days	a new- onset rash, scaly erythema on the right lower leg, hypotension (87/59 mm Hg) with heart rate at 113b. p.m, mild edema of the lower extremities	topical corticosteroids, an antihistamine, intravenous fluids and oral prednisolone	Recovery	3 weeks

(*Continued*)

Table 1. (Continued).

Reference	Year/ Region	Age/ Gender	Past medical history	MGUS	Vaccine type/times	Time of onset after vaccination	Clinical presentation	Treatment	Outcome	Course of disease
Akiyama Y et al.[17]	2023/ Japan	60/M	SCLS	IgG κ	Pfizer-BioNTech mRNA vaccine /2nd	1 days	fever, malaise, hypourocrinia, right leg edema, nausea, dizziness, dyspnea on exertion and paresthesia, hypotension（97/50 mmHg）with heart rate at 114b.p.m	fluid therapy	Recovery	5 days
Tanabe M et al.[18]	2021/ Japan	60/F	SCLS and cardiac arrest	None	Pfizer-BioNTech mRNA vaccine /2nd	2 days	fever, dyspnea, nausea and hypotension (81/60 mm Hg) with heart rate at 122 b.p.m	fluid therapy and intubate	Recovery	18 days
Araki T et al.[19]	2022/ Japan	53/F	None	None	Pfizer-BioNTech mRNA vaccine /2nd	4 days	Fever, general malaise, loss of appetite worsened and hypotension (SP 66 mm Hg) with heart rate at 139 b.p.m	Intravenous corticosteroids (methylprednisolone, 500 mg twice a day) and vasopressin	Recovery	23 days
Madala N et al.[20]	2022/ USA	56F	Unknown	None	Pfizer-BioNTech mRNA vaccine /2nd	3 weeks	ower extremity weakness, fever, shortness of breath and hypotension (80/60 mmHg)	intravenous fluids, albumin, vasopressors, steroids, intubation, continuous renal replacement therapy and intravenous immunoglobulin	Died	3 days
Inoue M et al.[21]	2021/ Japan	40/F	None	IgG λ	Pfizer-BioNTech mRNA vaccine /2nd	4 days	generalised malaise, chest discomfort, anasarca and hypotension (86/52 mm Hg) with heart rate at 129 b.p.m	1000 mg/day of methylprednisolone for 3 days and 50 g of intravenous immunoglobulin (1 g/kg), anticoagulation therapy with intravenous unfractionated heparin	Recovery	12 days
Choi GJ et al.[22]	2021/ South Korea	38/M	Smoldering multiple myeloma and SCLS	Multiple myeloma	Johnson & Johnson, Janssen /1st	12 hours	fever, chills, myalgia, nausea, recurrent vomiting, general weakness and hypotension (60/40 mm Hg) with heart rate at 132 b.p.m	broad-spectrum antimicrobials, intravenous fluids and inotropes	Died	2 days
Kosaka A et al.[23]	2023/ Japan	61/F	Smoldering multiple myeloma and SCLS	IgG λ（2020）	Pfizer-BioNTech mRNA vaccine /2nd	1 year	fever, sore throat, headache, and muscle pain	3000 mL crystalloid, noradrenalin, vasopressin, aminophylline and methylprednisolone	Died	2 days
		58/M	hypertension, asthma, chronic obstructive pulmonary disease overlap syndrome, pneumothorax and acute respiratory distress syndrome	None	COVID-19 mRNA vaccine /4th	none	fever, cough, and sore throat	remdesivir, fluid resuscitation, piperacillin/tazobactam, vancomyci, dexamethasone Sodium bicarbonate, glucose-insulin therapy and 5 g/day of intravenous immunoglobulin	Recovery	3 days

Abbreviations: SCLS: systemic capillary leak syndrome; M: male; F: female; MGUS: monoclonal gammopathy of undetermined significance.

Table 2. Physical and laboratory examination of 15 patients from case reports.

	Physical examination	Laboratory examination			
Reference	Blood pressure, mmHg	Hemoglobin, g/L	Hematocrit, %	Creatinine, mg/dL	Albumin, g/L
Normal	90–139/60–89	137–168	40–52	0.7–1.2	35–50
Buj M et al.[13]	Y(72/51 mmHg)	236	70	3.8	17
Matheny M et al.[14]	Y	201	62	2.59	11
	Y	233	68.6	1.5	20
	Y	199	62.8	2.4	23
Robichaud J et al.[8]	N(93/60 mmHg)	224	65	1.5	28
Yang C et al.[15]	Y	176	52	None	28
Yatsuzuka K et al.[16]	Y(87/59 mmHg)	None	None	1.65	26
Akiyama Y et al.[17]	Y(97/50 mmHg)	222	67.5	1.51	32
Tanabe M et al.[18]	Y(81/60 mmHg)	156	47	0.93	36
Araki T et al.[19]	Y(66/-mmHg)	208	None	None	8
Madala N et al.[20]	Y(80/60 mmHg)	None	None	None	None
Inoue M et al.[21]	Y(86/52 mmHg)	241	72.3	0.22	18
Choi GJ et al.[22]	Y(60/40 mmHg)	227	63.7	2	33
Kosaka A et al.[23]	N(110/71 mmHg)	123	36.7	0.84	36
	N(169/119 mmHg)	217	62.9	1.86	None

Y means the patient had hypotension.
N means the patient had not hypotension.

Results

Basic information

The basic information of the 15 cases included in the ultimate analysis is as follows. The majority of the 15 patients were from Asia (7 from Japan and 1 from South Korea), with the rest from North America (4 from the United States of America and 2 from Canada) and Europe (1 from Spain). The mean age of the 15 patients was 53 years old, the median age was 56 years old, and the range was 30 years old (36–66 years old). Among them, 7 were female (mean age 51.6 years, median age 58 years) and 8 were male (mean age 54.3 years, median age 54.5 years). Regarding past medical history, 4 patients ever had SCLS and 2 patients had hypertension. All patients were vaccinated with COVID-19 vaccine, including 9 cases of Pfizer-BioNTech mRNA vaccine jointly developed by Pfizer and BioNTech. 2 cases were vaccinated with Johnson & Johnson, Janssen, a vaccine developed by the Dutch arm of the US pharmaceutical company Johnson & Johnson Group. 2 cases were vaccinated with the Oxford-AstraZeneca AZD1222 COVID-19 vaccine developed jointly by AstraZeneca and Oxford University, and 1 case was vaccinated with the Moderna COVID-19 vaccine developed by Moderna. Among them, most of the patients (10 cases) developed SCLS after the second vaccination, followed by 3 cases after the first vaccination, 1 case after the fourth vaccination, and 1 case did not mention the vaccination times.

Clinical characteristics

We collected and summarized the clinical presentations of 15 patients, detailed in Table 1. Most of the patients (11 cases) developed SCLS within one week of vaccination, of which 4 cases developed within one day of vaccination, 4 cases developed two days later, and 2 cases developed four days later. Of the 15 patients, 8 experienced generalized discomfort and pain. 9 patients developed fever. As many as 13 patients presented hypotension, and 11 of them showed tachycardia. Respiratory-related symptoms were found in 8 patients, including wheezing and dyspnea. 7 patients had gastrointestinal symptoms, including nausea, vomiting and diarrhea.

Physical & laboratory examination

The results of physical and laboratory tests that are highly associated with SCLS and commonly performed are presented in Table 2. Among the 15 cases included, hemoglobin was measured in 13 patients, with 11 showing elevated levels. Hematocrit was measured in 12 patients, of which 9 patients had elevated hematocrit. Creatinine was measured in 12 patients, with 9 showing increases. Albumin was measured in 13 patients, 11 of whom had low albumin. All patients had their blood pressure measured and 13 of them had hypotension.

Treatment

The treatment and prognosis summary for 15 patients is presented in Table 1. Drug therapy included intravenous infusion (9 cases), corticosteroid therapy (9 cases), intravenous immunoglobulin (6 cases), vasopressors (6 cases), antibiotic therapy (5 cases), renal replacement therapy (3 cases), crystalloid therapy (4 cases), and albumin therapy (3 cases). Two patients received intubation treatment, and one patient was treated with anticoagulation therapy plus intravenous administration of unfractionated heparin.

Eleven patients were successfully cured, while four patients died due to ineffective treatment, specifically due to additional SCLS complications worsening (case 2), cardiac arrest (case 11), worsening hypotensive shock (case 13), and secondary pulmonary edema with respiratory failure (case 14). Among those who recovered and were discharged, the duration of illness ranged from two days to three weeks.

Discussion

In summary, we have collected and discussed a series of cases of SCLS following COVID-19 vaccination, describing the rare

association between systemic capillary leakage and COVID-19 vaccine administration. SCLS is a rare disorder with an unclear etiology, characterized by recurrent and unpredictable episodes of capillary leakage, although it is thought to be caused by a combination of endothelial contraction, cell apoptosis, and damage.

Because the symptoms and signs of SCLS are very similar to many other diseases, diagnosing SCLS requires clinical evaluation and the exclusion of other conditions that cause similar symptoms and signs, such as vascular edema, allergic reactions, and sepsis.[7] The SCLS diagnostic triad is composed of the "3 Hs:" ①hypotension (typically systolic blood pressure <90 mm Hg); ② hemoconcentration (men >49% to 50% and 43% to 45% in women, or hemoglobin >20 g/dL); ③hypoalbuminemia (serum albumin <3.0 g/dL) in the absence of secondary causes for such abnormalities.[24] After fluid resuscitation, severe, rapidly developing systemic edema of the face, trunk, and extremities usually occurs,[7] which matches the clinical presentation of our cases. However, these clinical criteria are nonspecific and not present in all cases, making the predictive diagnosis of SCLS challenging. Research reports suggest that mRNA vaccines pose a greater risk than viral vector vaccines, although they perform well in preventing COVID-19. This is largely consistent with the statistical results regarding the types of vaccines administered to the patients.[10]

According to what we found, most of the patients presented with prodromal symptoms such as weakness, dizziness, and extreme fatigue early in the course of the disease, which is consistent with the presentation of 25 patients suffering from systemic capillary leakage syndrome from 1981 to 2008 as documented by Prashant Kapoor et al.[25] In patients with capillary leakage syndrome, the increased permeability of the capillaries leads to the outflow of protein-rich fluid from the capillaries into the interstitial space, which is a key factor causing hypotension in most patients.[6] In order to compensate for the hypotension-induced perfusion deficit in a short period of time, the heart rate of the patient will accelerate, which leads to the simultaneous occurrence of hypotension and tachycardia.

It is worth noting that respiratory disorders such as dyspnea and chest pain were present in more than half of the patients we recorded. This presentation may be associated with exudative pleural effusion, as confirmed in previous studies.[26] In the presence of hypovolemia, secondary activation of the renin, angiotensin, and aldosterone systems will further promote sodium and water retention and cause generalized multisystem edema. If the edema occurs in the gastrointestinal tract, the patient may experience abdominal pain, nausea, and vomiting. This mechanism explains the presence of gastrointestinal reactions in close to half of the patients we documented.[6] In terms of clinical presentation, capillary leakage, sepsis and septicemia can all lead to fever and shock, which need to be treated by empirical antimicrobials and identified by cultures and clinical evaluation.[26] Also, anaphylaxis can interfere with the diagnosis and requires further differentiation.[27]

In laboratory examinations, when SCLS occurs, protein-rich plasma is lost from the blood vessels to the surrounding interstitial fluid, resulting in hypoproteinemia. Albumin is the most abundant protein in serum. Studies have shown that trauma may be a trigger for SCLS. Following injury, liver protein synthesis changes from albumin to acute phase reactants and immune mediators,[28] which makes hypoproteinemia more dramatic and stubborn. Low albumin levels are strongly positively correlated with adverse disease outcomes.[29] In contrast, erythrocytes are larger and usually remain within blood vessels, so when plasma is lost, the relative concentration of erythrocytes and the hemoglobin in them increases, resulting in hemoconcentration. Hemoglobin levels typically exceed 20 g/dL and do not improve with intravenous saline, making SCLS easily misdiagnosed as polycythemia vera,[30] and possibly resulting in ineffective bloodletting therapy[31] that aggravates the condition. It is worth nothing that elevated hemoglobin levels may be masked by underlying anemia,[32] and patients with slower-developing SCLS may not show hemoconcentration.[6] Acute kidney injury (AKI) is the most common organ injury in SCLS,[33] which is often caused by reduced renal perfusion due to low blood volume.[34] AKI is characterized by a sharp drop in glomerular filtration rate followed by an increase in serum creatinine concentration and oliguria.[35] Gosling et al. showed that microalbuminuria (urinary protein to creatinine ratio, ACR) can reflect rapid changes in systemic capillary permeability and is an indicator of the severity of SCLS.[36] In our case, most patients had decreased albumin levels, increased hematocrit levels, elevated hemoglobin levels, and elevated creatinine levels, which were consistent with the above analysis and the diagnostic indicators of SCLS.

Since the SCLS we studied is a rare adverse event that may be caused by the COVID-19 vaccines, the treatment strategies were based on clinical data observation rather than control experiments. Although many of our patients have undergone corticosteroid therapy, the related drug trials have not been shown to be effective. In most patients, steroids cannot prevent the progression of the disease.[7] This syndrome has a fatal risk, with nearly one-third of our cases resulting in death. At the same time, SCLS is also self-limiting, and conservative treatment is essential for patients in the acute phase.[37] Because the pathological mechanism of SCLS is the transfer of protein and liquid caused by high permeability of capillaries, resulting in blood concentration and low serum albumin, liquid therapy is not effective in acute attacks and may also aggravate pulmonary edema. Fishel et al. believed that when the capillary leakage syndrome was caused by infection or inflammation, the use of excessive crystal solution treatment might cause pulmonary edema and hinder tissue oxygen supply. At this time, the use of albumin and other colloidal solution treatment may be more effective.[38]

Most patients received IVIg treatment. Previous studies have shown that IVIg is well-tolerated, can prevent acute flares of systemic capillary leak syndrome, and helps to reduce the frequency of SCLS-related residual symptoms such as fatigue, general discomfort and limb swelling.[39] IVIg also has the characteristics of anti-cytokines and immune regulation, and can inhibit the synthesis of interleukins, especially IL-2, which may be related to the mechanism of SCLS.[40] By interacting with complements, IVIg can also reduce complement-mediated tissue damage by removing the active components of the scavenger and transferring complements to target

cells.[41] However, the optimal treatment regimen, dose and duration of IVIg still need to be further studied. It is confirmed that IVIg may be considered as frontline therapy for subjects with a clear-cut diagnosis of SCLS and recurrent attacks. Given the rarity of SCLS, we need more patient treatment experience to further determine whether IVIg can be used as the primary treatment.[39,42]

The specific mechanism of SCLS induced by COVID-19 vaccines is not completely clear, but literature suggests that both viral vector and mRNA COVID-19 vaccines induce strong activation of CD8+ T cells and CD4+ T cells, as well as the production of TNF-α, IFN-γ, and IL-2[10]. Elevated IL-2 plays an important role in the inflammatory response and cytokine storm in COVID-19 patients.[43] At the same time, IL-2 can enhance the production of nitric oxide synthase (NOS) and induce the production of NO, which directly or indirectly damages capillaries and leads to fluid leakage.[44] Lim WC et al. showed that the expression of IL-6, G-CSF and GM-CSF in endothelial cells increased significantly under the synergistic effect of TNF-α and IFN-γ.[45] In addition, Karki R et al. showed that the synergistic effect of TNF-α and IFN-γ could directly cause endothelial cell injury.[46] IL-6 directly affects vascular endothelial cells, produces multiple types of cytokines and chemokines, and activates the coagulation cascade, resulting in endothelial dysregulation characterized by coagulation disorders and vascular leakage,[47] while triggering cytokine storms. Cytokine storms will activate more immune cells, further aggravating endothelial cell injury and SCLS, forming a vicious cycle (Figure 2).

We observed the occurrence of monoclonal gammopathy of undetermined significance (MGUS） with unknown significance in the collected cases. MGUS is defined as a plasma cell dyscrasia with a predominant increase of the IgG immunoglobulin fraction without end-organ damage, and the clinical absence of symptoms attributable to a plasma cell proliferative disorder like hypercalcemia, renal insufficiency, anemia, and bone lesions.[48] And three of them had a past medical history of MGUS, and five patients were diagnosed with MGUS in their present medical history. Different from other vascular leakage syndromes, this disease is currently only found in adult SCLS patients. It is reported that up to 79% of adult SCLS patients are diagnosed with MGUS,[49] corresponding with the data we collected, which has not been observed in the pediatric cohort. The most common monoclonal immune protein is IgG kappa.

Capillary leakage can also be caused by a variety of diseases, such as autoimmune diseases, differentiation syndrome, graft syndrome, etc. Not only that, some monoclonal antibodies and anticancer drugs, including some interleukins, can also cause capillary leakage, often accompanied by AKI. In addition to hypotension, cytokines may play an important role in the pathophysiology of AKI caused by capillary syndrome.[7] Whole-exome sequencing of patients and their unaffected first-degree relatives revealed rare compound heterozygous pathogenic nucleotide variations that may follow recessive inheritance, such as ZNF407 (both nuclear binding proteins), NPC1L1, TECPR1 (all protein binding genes), which is helpful for the study of the pathogenesis of SCLS. Genetic analysis showed that the phenotype of SCLS could not be explained by a single gene

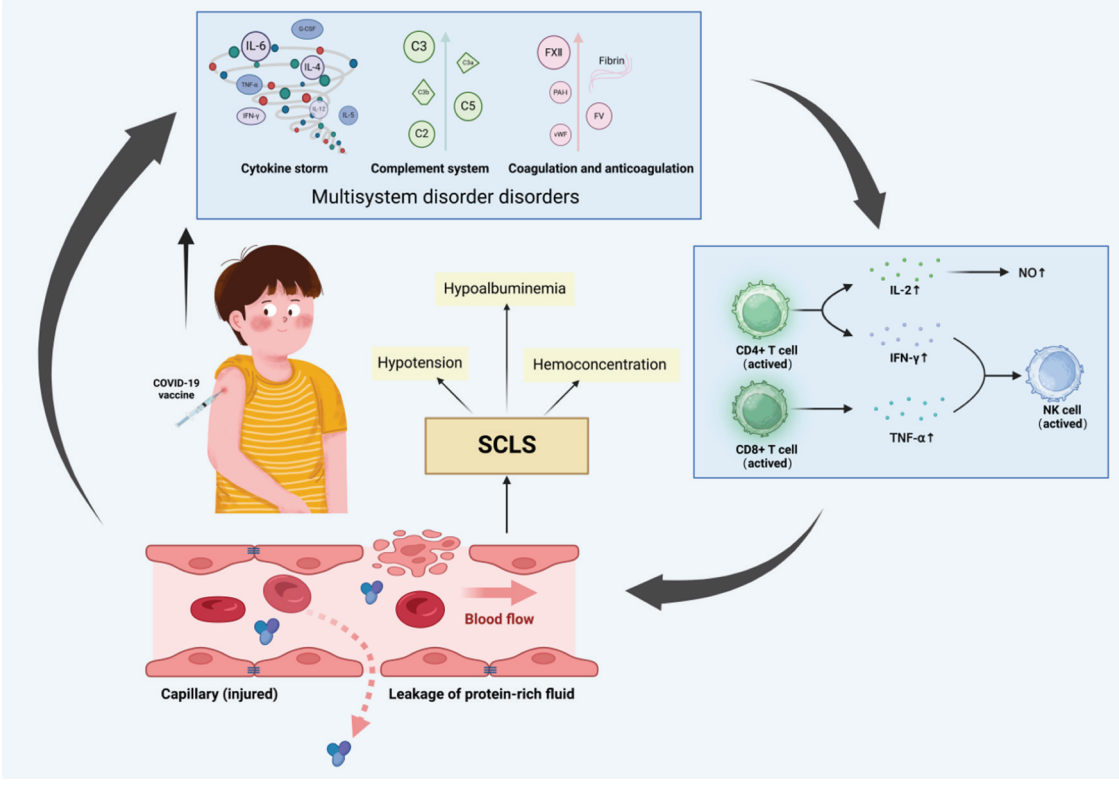

Figure 2. Schematic mechanism of systemic capillary leak syndrome following COVID-19 vaccination. Abbreviation: SCLS: systemic capillary leak syndrome; IL: interleukin; IFN: interferon; TNF: tumor necrosis factor; NK cell: natural killer cell.

or a germline exome mutation of a known pathway. The results cannot rule out that one of the causes of SCLS is genetic variation. Rare variations of various genes have been found in individual patients in the study cohort. A large number of gene interactions may produce a common phenotype leading to the occurrence and development of SCLS. In addition, genetic changes in non-coding regions such as intron sequence variations or epigenetic modifications may also induce SCLS. Confirmation of this view requires additional methods, such as whole genome sequencing or DNA methylation analysis. Another possibility is that SCLS may be caused by a complex interaction of two or more gene variants. However, current studies have not confirmed or overturned the more complex genetic regulatory mechanisms that may exist in SCLS.[50] An interesting finding is that most of the patients in our cases showed SCLS after the second dose of vaccination. The specific reason is not clear, and further research is needed. Additionally, one-third of patients have a history of SCLS and are re-attacked after being vaccinated against COVID-19, which may also become a new entry point for clinicians in the diagnosis of SCLS.

Conclusion

In this paper, we systematically studied the SCLS reported after COVID-19 vaccination, and its pathogenesis is still unclear. When patients have acute fever after vaccination with COVID-19 vaccines and are accompanied by hypotension, vomiting, physical discomfort, and tachycardia, in addition to common adverse reactions such as sepsis, allergic reactions, and infections, clinicians also need to pay attention to SCLS. SCLS can be differentiated by the typical triad of hypotension, blood concentration, and hypoalbuminemia. Early diagnosis are crucial for the prognosis of COVID-19 vaccination in SCLS patients. In particular, clinical risk assessment and safety monitoring should be performed in patients with a history of SCLS who receive COVID-19 vaccinations. When carrying out the second dose of vaccination, we should also pay more attention to the occurrence of rare diseases such as SCLS.

Author contribution

Chengjie Zhao: Conceptualization, Methodology, Investigation, Writing – Original Draft. **Ruirui Xue**: Methodology, Investigation, Writing – Original Draft, Visualization. **Kaile Zhao**: Methodology, Investigation, Writing – Original Draft. **Ruoyan Lei**: Methodology, Investigation. **Mingyi Zhao**: Conceptualization, Writing – Original Draft, Funding acquisition. **Lin Liu**: Supervision, Writing – Review & Editing, Funding acquisition.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Abbreviation

SCLS	systemic capillary leak syndrome
AKI	acute kidney injury
ACR	microalbuminuria
IVIg	intravenous immunoglobulin
IL	interleukin
IFN	interferon
TNF	tumor necrosis factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
G-CSF	H-granulocyte colony-stimulating factor
MGUS	monoclonal gammopathy of undetermined significance

Data availability statement

All data generated in this article are included in the paper and supplementary materials.

Ethical approval statement

The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

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