

# Capillary Leak Syndrome

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نفروتوکسین‌ها و کلیه

Kidney and Nephrotoxins

۱۳-۱۵ مهر ۱۴۰۱-تهران

- ✓ **Systemic capillary leak syndrome** (SCLS) is a rare disorder that is characterized by hypotension, hemoconcentration, and hypoalbuminemia.
- ✓ SCLS is associated with increased permeability of the capillary endothelium to proteins.
- ✓ Clinical features: **edema, hypotension, hypoalbuminemia, or hemoconcentration.**
- ✓ These clinical features are nonspecific and not present in all cases.

J. Clin. Med. 2019, 8, 143; doi:10.3390/jcm8020143



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- ✓ Most cases of CLS are classified as idiopathic forms, also called **Clarkson's disease**.
- ✓ It may also develop as a secondary form, preceded by **autoimmune** diseases, **infections**, **snakebites**, and **drugs**.
- ✓ **Cancer and chemotherapy** are also considered to be important causes of secondary CLS.

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✓ Attacks of ISCLS typically demonstrate **three phases**:



prodromal



leak



recovery phase

✓ The **frequency and severity** of attacks vary significantly.

✓ The **prodromal phase** is characterized by symptoms such as fatigue, nausea, myalgia, and a sudden increase in body weight.

[Remya Rajan et al, Tropical Health and Education Trust. 2021 , Volume 51, Issue 2](#)  
[Case report](#)



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- ✓ This is followed by a **leak phase** within **one to four days**, which is characterized by the **triad** of **hypotension**, **haemoconcentration**, and **hypoalbuminemia**.
- ✓ In the **recovery phase**, the extravasated fluid is recruited into the intravascular compartment, and the patient is at an **increased risk for volume overload**.

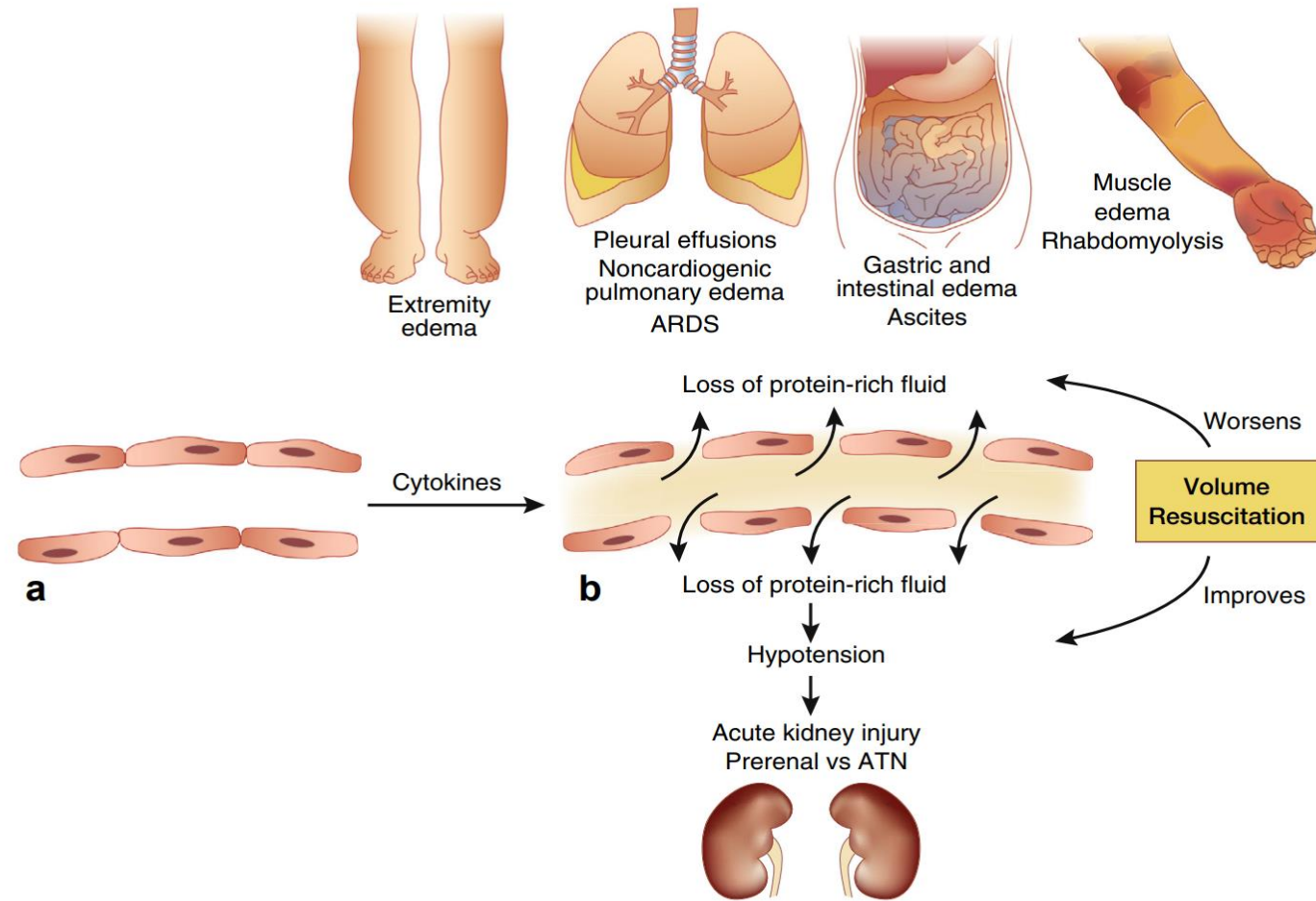
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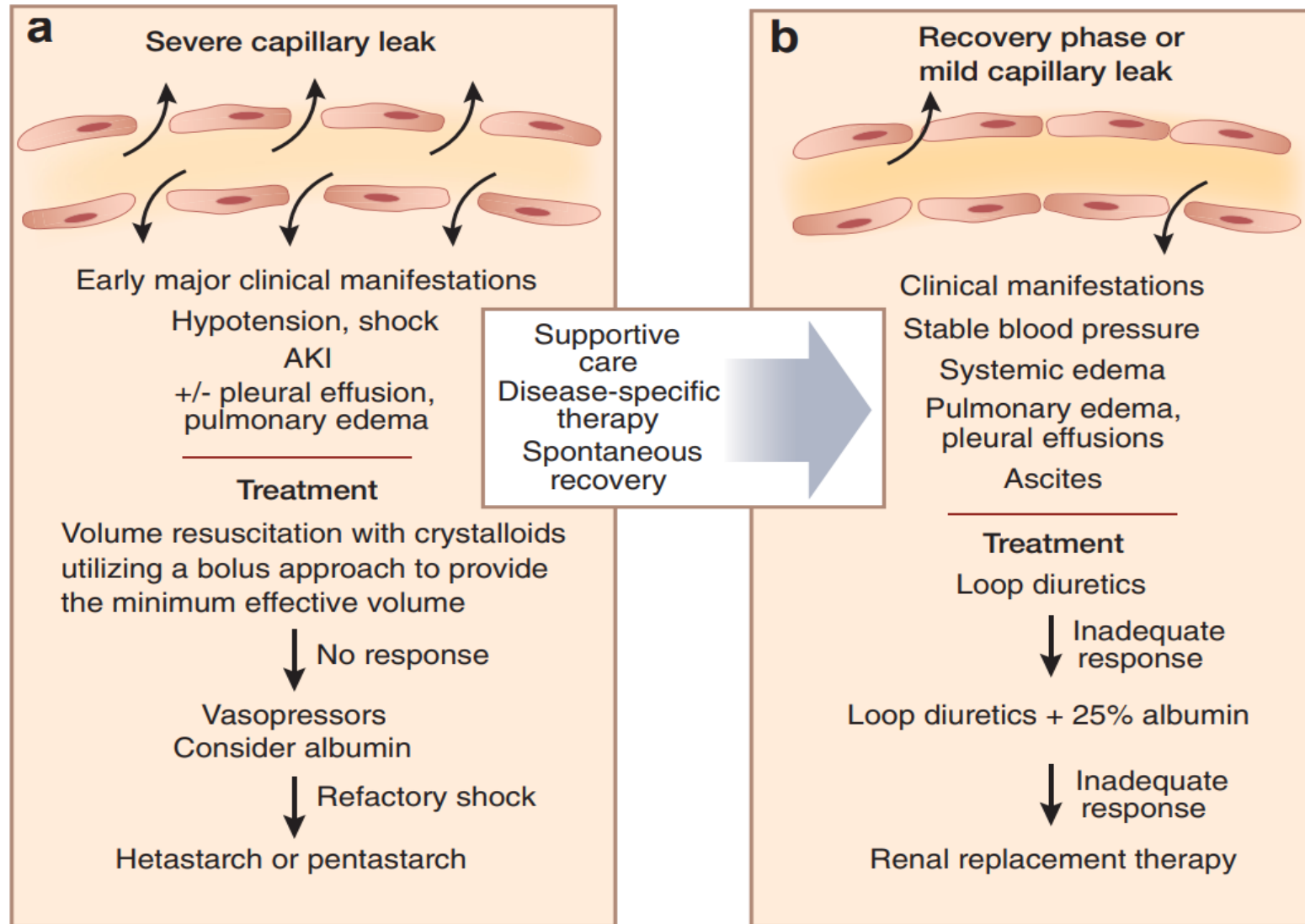
Eric Siddal et al, Kidney International (2017) 92, 37–46



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## Original Article

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# Clinical Presentation, Management, and Prognostic Factors of Idiopathic Systemic Capillary Leak Syndrome: A Systematic Review

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Tae Seong Eo, MS<sup>a</sup>, Kyung Ju Chun, MS<sup>b</sup>, Su Jung Hong, MS<sup>c</sup>, Ji Young Kim, MS<sup>d</sup>, I. Re Lee, MD<sup>e,f</sup>, Keum Hwa Lee, MD<sup>e,f</sup>, Michael Eisenhut, MD, FRCPCH, FRCP<sup>g</sup>, Andreas Kronbichler, MD, PhD<sup>h</sup>, and Jae Il Shin, MD, PhD<sup>e,f,i</sup> *Seoul, Pocheon, Jeonju, and Daejeon, Korea; Luton, United Kingdom; and Innsbruck, Austria*

Eo et al, J ALLERGY CLIN IMMUNOL PRACT MONTH 2017



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- ✓ A total of 133 case reports (161 patients) and 5 case series (102 patients) of idiopathic systemic capillary leak syndrome were included.
- ✓ RESULTS: Patients had hypotension (81.4%), edema (64.6%), and previous flu-like illness (34.2%)
- ✓ Thirty-seven patients died (23%) mainly because of systemic capillary leak syndrome itself (78.4%).

Eo et al, J ALLERGY CLIN IMMUNOL PRACT MONTH 2017 2



✓ SCLS can be caused by **cancer**, **infections**, **drugs** but can occur as **idiopathic** SCLS after secondary causes are ruled out.



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- ✓ Most patients with idiopathic SCLS have a concomitant presence of monoclonal gammopathy, which is not a mandatory criterion for diagnosis but aids in the diagnosis.
- ✓ In the prodromal phase, there is a trigger for systemic leakage. This is most frequently a viral infection

Eo et al, J ALLERGY CLIN IMMUNOL PRACT MONTH 2017, Volume 6, Issue 2



**TABLE VII.** Estimated 1-, 5-, and 10-y survival rate of patients treated with prophylactic treatment

Treatment	1-y survival rate	5-y survival rate	10-y survival rate
Overall	88.8%	71.8%	55%
With IVIG	100%	93.8%	93.8%
Without IVIG	86.5%	67.2%	48.5%
With $\beta 2$ agonists	98%	82.7%	70.7%
Without $\beta 2$ agonists	83%	79.6%	45.2%
With methylxanthines	96.2%	88.4%	76%
Without methylxanthines	83.5%	59.4%	40.5%



# Diagnostic and therapeutic considerations in idiopathic systemic capillary leak syndrome: a case report

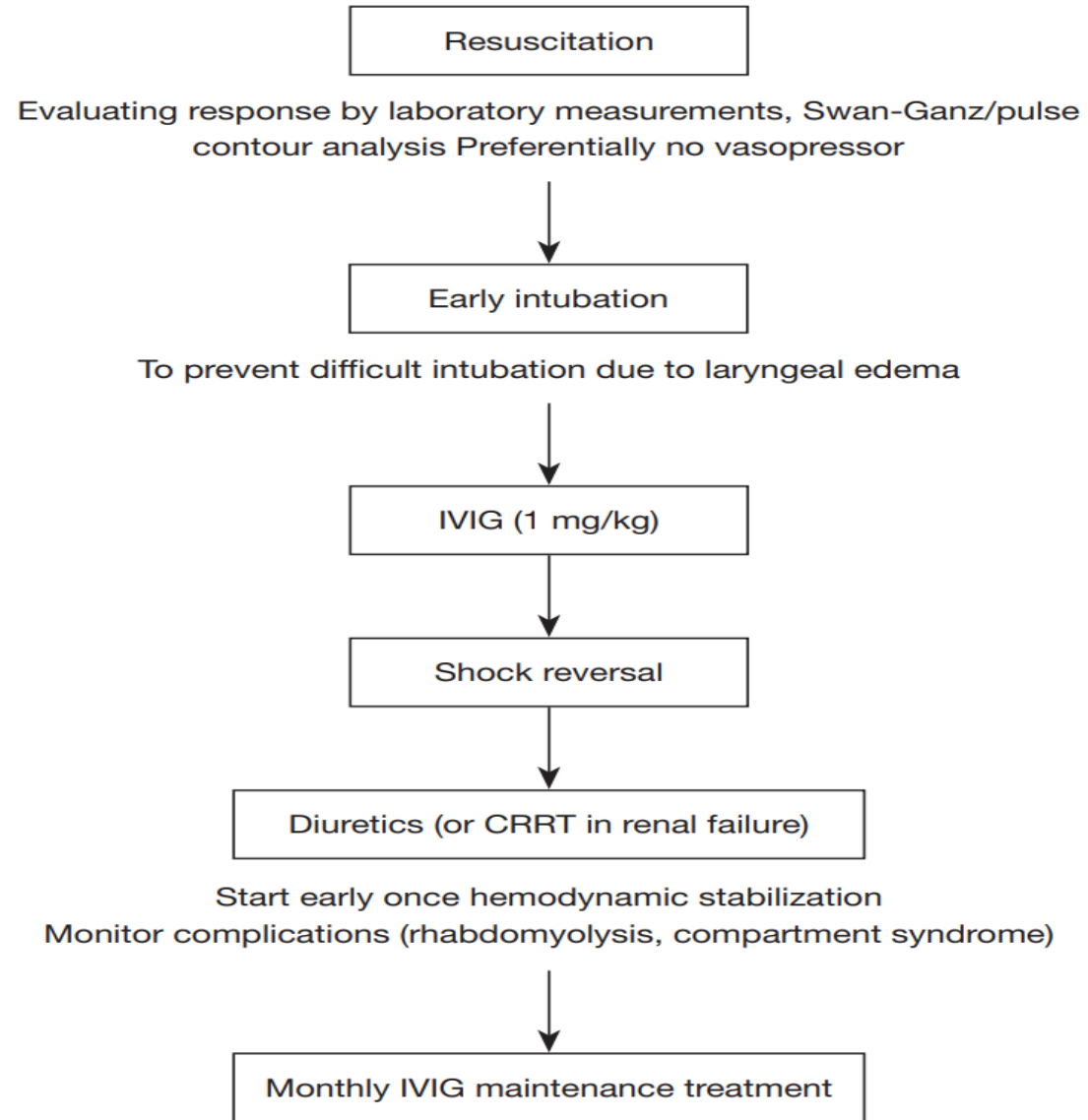
Marloes Houterman<sup>1</sup>, Dennis Ellenbroek<sup>1</sup>, Jelmer K. Humalda<sup>2</sup>, Johannes G. van der Hoeven<sup>1</sup>,  
Bart P. Ramakers<sup>1</sup>

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J Emerg Crit Care Med 2022 | <https://dx.doi.org/10.21037/jeccm-22-22>





**Figure 2** Decision making tool for the treatment of SCLS. SCLS, systemic capillary leak syndrome; IVIg, intravenous immunoglobulins; CRRT, continuous renal replacement therapy.





Journal of  
*Clinical Medicine*



*Article*

# Systemic Capillary Leak Syndrome (Clarkson Syndrome) in Cancer Patients: A Systematic Review

Jae Il Shin <sup>1,2,3,\*</sup> , Keum Hwa Lee <sup>1,2</sup>, I. Re Lee <sup>1,2</sup>, Ji Hyun Oh <sup>4</sup>, Dong Wook Kim <sup>1</sup>,  
Jae Won Shin <sup>1</sup>, Tae Seong Eo <sup>1</sup>, Andreas Kronbichler <sup>5</sup> , Michael Eisenhut <sup>6</sup> and  
Hans J. van der Vliet <sup>7</sup>

They identified 62 case reports in 53 articles that met the inclusion criteria for this systematic review

Shin et al, J. Clin. Med. 2018, 7, 418; doi:10.3390/jcm7110418



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# SCLS and Cancer

✓ SCLS was associated with



cancer itself in 43.6%

anti-cancer agents in 51.6%

BMT in 4.8%



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# SCLS and Cancer

✓ The most common associated malignancies were

- ✓ hematologic (61.3%)
- ✓ non-Hodgkin lymphoma (22.7%)
- ✓ multiple myeloma (12.9%)



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Variables	Observed Number of Patients (%) among Total Number of Patients ( $n = 62$ )
Acute lymphoblastic leukemia	2 (3.2%)
Acute myeloid leukemia	1 (1.6%)
Chronic myelocytic leukemia	2 (3.2%)
Plasma cell leukemia	1 (1.6%)
Malignant lymphoma of tonsil	1 (1.6%)
Malignant lymphoma of cervical cord	1 (1.6%)
Fanconi anemia	1 (1.6%)
Non-hematologic malignancy	24 (38.7%)
Renal cell carcinoma	4 (6.5%)
Colorectal cancer	4 (6.5%)
Pancreatic cancer	3 (4.8%)
Hepatic carcinoma	2 (3.2%)
Non-small cell lung cancer	2 (3.2%)
Breast cancer	2 (3.2%)
Pituitary adenoma	1 (1.6%)
Primitive neuroectodermal tumor	1 (1.6%)
Distal common bile duct cancer	1 (1.6%)
Nasopharyngeal cancer	1 (1.6%)
Ovarian cystic teratoma	1 (1.6%)
Sarcoma	1 (1.6%)
Myxofibroma of maxilla	1 (1.6%)



✓ **Main presenting symptoms** and findings using physical and radiological examination of patients with SCLS included :



peripheral edema (67.7%)



hypotension (32.2%),



pleural effusion (29.0%)



dyspnea (27.4%)



ascites (22.7%)



oliguria (22.7%)



weight gain (21.0%)



fever (17.7%)



pulmonary edema (11.3%)



# Laboratory Findings:

- ✓ leukocytosis was observed in 40.1%
- ✓ anemia in 48.0%
- ✓ hemoconcentration in 63.6%
- ✓ thrombocytopenia in 73.7%
- ✓ hypoalbuminemia in 96.9%



# SCLS and Anticancer Agents

- ✓ Among anti-cancer agents,
- ✓ (G-CSF) (14.6%)
- ✓ interleukin (IL)-2 (11.4%)



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**Table 2.** Etiologies of cancer patients with systemic capillary leak syndrome.

Variables	Total Number of Patients ( <i>n</i> = 62) Observed Number of Patients (%)
Cancer *	27 (43.6%)
BMT-related GVHD	3 (4.8%)
Anti-cancer agents	32 (51.6%)
G-CSF	9 (14.6%)
Interleukin-2	7 (11.4%)
Denileukin diftitox	2 (3.2%)
Gemcitabine	2 (3.2%)
MINE regimen	2 (3.2%)
Gemcitabine + paclitaxel	1 (1.6%)
Doxorubicin	1 (1.6%)
Bortezomib	1 (1.6%)
Clofarabine	1 (1.6%)
Cyclosporin A	1 (1.6%)
Trastuzumab	1 (1.6%)
Busulfan + etoposide + nimustine	1 (1.6%)
Pemetrexed	1 (1.6%)
Oxaliplatin	1 (1.6%)
Oxaliplatin + capecitabine	1 (1.6%)

# Pathogenic Molecules:

- ✓ **No study** has investigated soluble factors or diagnostic markers of cancer-related SCLS.
- ✓ Some pathogenic molecules in idiopathic SCLS :
- ✓ **Increased numbers of circulating CD25+ T cells**, perivascular infiltrations of mononuclear cells with an increased number of CD8+ T lymphocytes
- ✓ **Endothelial injury and apoptosis**
- ✓ **Increased serum cytokine levels** such as elevated serum chemokine (C-X-C motif) ligand (CXCL)10, chemokine ligand 2 (CCL2), IL-1 $\beta$ , IL-6, IL-8, IL-12, and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ )
- ✓ **high levels of plasma (VEGF) and angiopoietin-2**





*Article*

# Incidence of Capillary Leak Syndrome as an Adverse Effect of Drugs in Cancer Patients: A Systematic Review and Meta-Analysis

Gwang Hun Jeong <sup>1</sup>, Keum Hwa Lee <sup>2,3,4</sup> , I Re Lee <sup>2,3</sup>, Ji Hyun Oh <sup>5</sup>, Dong Wook Kim <sup>2</sup>, Jae Won Shin <sup>2</sup>, Andreas Kronbichler <sup>6</sup> , Michael Eisenhut <sup>7</sup>, Hans J. van der Vliet <sup>8</sup>, Omar Abdel-Rahman <sup>9,10</sup> , Brendon Stubbs <sup>11,12,13</sup>, Marco Solmi <sup>14</sup>, Nicola Veronese <sup>15</sup> , Elena Dragioti <sup>16</sup> , Ai Koyanagi <sup>17</sup>, Joaquim Radua <sup>18,19,20,21</sup> and Jae Il Shin <sup>2,3,4,\*</sup>

J. Clin. Med. 2019, 8, 143; doi:10.3390/jcm8020143





- ✓ There were **62 clinical studies** that reported on the incidence of CLS in patients receiving **anti-cancer treatments** or **after BMT**
- ✓ The **incidence of CLS by IL-2** was **34.7%** by overall estimation and **43.9%** by meta-analysis.
- ✓ **No correlations were found between the dose of IL-2 and the overall incidence of CLS.**



# Incidence of SCLS

- ✓ The incidence of CLS in patients treated **with IL-2 with other agents was 29.1%** by overall estimation and **32.0%** by meta-analysis.
- ✓ We found that the **highest incidence of CLS (80.5% and 100%)** was observed when **IL-2 was combined with IFN-alpha.**



- ✓ The **incidence of CLS** in patients who received **IL-2 + bevacizumab** (IL-2 dose: 9 µg/kg) was **100%**.
- ✓ In cases with concomitant **IL-2 + 5-FU** treatment, the incidence of CLS varied from 6.3% to 25.0%, resulting in **17.5% by overall estimation** and 17.1% by meta-analysis
- ✓ In the **IL-2 + imatinib mesylate** group, there was a **dose-related** increase in the incidence of CLS (**0% → 9% → 33.3%**)



**Table 3.** Meta-analyses on the incidence of capillary leak syndrome induced by various anti-cancer drugs or after BMT in cancer patients.

Causative Drugs	Number of Studies	Total Number of Patients	Number of CLS	Incidence of CLS (Overall)	Incidence of CLS by Meta-Analysis (95%CI)	Heterogeneity I <sup>2</sup> (p Value)	Incidence of CLS Median (Ranges)
IL-2	18	703	244	34.7%	29.5–58.9)	92.6% ( $p < 0.0001$ )	32.4% (5.3–100)
IL-2 with other agents	13	405	118	29.1%	15.6–51.1)	91.1% ( $p < 0.0001$ )	16.7% (0–100)
IL-2 + IFN-alpha 2a	2	55	47	85.5%	64.1–100)	80.0% ( $p = 0.0255$ )	90.3% (80.5–100)
IL-2 + imatinib mesylate	3	17	2	11.8%	3.1–33.4)	0% ( $p = 0.4889$ )	9.0% (0–33.3)
IL-2 + bevacizumab	1	4	4	100.0%	-	-	-
Gemcitabine	3	86	3	3.5%	3.7–37.4)	56.1% ( $p = 0.1312$ )	33.3% (6.3–25.0)
SS1P	2	58	15	25.9%	24.3–61.4)	0% ( $p = 0.8266$ )	42.2% (40–44.4)
Anti-CD agents	13	221	75	33.9%	-	-	-
Anti-CD22	4	59	24	40.7%	4.6–17.6)	0% ( $p = 0.5802$ )	7.1% (6.8–15.0)
Anti-CD19 + anti-CD22	2	42	8	19.0%	4.9% (1.4–10.3)	0% ( $p = 0.9273$ )	3.7% (2.8–4.3)
Anti-CD25	3	60	22	36.7%	26.9 (0.00–78.6)	94.5% ( $p < 0.0001$ )	30.1 (5.9–54.2)
BMT	7	417	88	21.1%	35.6% (16.1–60.0)	91.8% ( $p < 0.0001$ )	20.0% (5.9–100)
Only BMT-related	3	163	53	32.5%	48.1% (6.3–91.7)	93.7% ( $p < 0.0001$ )	44.1% (11.5–100)
BMT with other agents	4	254	35	13.8%	17.8% (2.7–42.2)	69.6% ( $p = 0.0699$ )	17.0% (5.9–28.0)

CLS: capillary leak syndrome, IL: interleukin, GM-CSF: granulocyte-macrophage colony-stimulating factor, 5-FU: 5-fluorouracil, SS1P: recombinant anti-mesothelin immunotoxin, CD: cluster of differentiation, BMT: bone marrow transplant.

- ✓ **Two studies** reported the incidence of CLS associated with the use of **IL-1 in combination with carboplatin** (one study, 40% CLS incidence) or **etoposide** (one study, 44.4%).
- ✓ The incidence of CLS by **GM-CSF** was 9.0% by overall estimation and 10.1% by meta-analysis



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IL-2 + bevacizumab	1	4	4	100.0%	-	-	-
IL-2 + 5-FU	2	40	7	17.5%	17.1% (3.7–37.4)	56.1% ( $p = 0.1312$ )	33.3% (6.3–25.0)
IL-1 with other agents	2	24	10	41.7%	42.3% (24.3–61.4)	0% ( $p = 0.8266$ )	42.2% (40–44.4)
GM-CSF	3	78	7	9.0%	10.1% (4.6–17.6)	-	7.1% (6.8–15.0)
Gemcitabine	3	86	3	3.5%	4.9% (1.4–10.3)	-	3.7% (2.8–4.3)
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- ✓ The incidence of CLS caused by **gemcitabine** was **3.5%** by overall estimation and 4.9% by meta-analysis.





- ✓ The incidence of CLS by various kinds of **anti-CD agents** was **33.9%** by overall estimation and **35.6%** by meta-analysis.
- ✓ The incidence of CLS by various kinds of **anti-CD22 mAb** was **40.7%** by overall estimation and **48.1%** by meta-analysis.
- ✓ It appeared that there was an increased incidence of CLS with an increasing treatment dose of **anti-CD22 mAb**
- ✓ .





- ✓ The addition of **anti-CD19 mAb to anti-CD22 mAb** treatment did not result in a further increase in the incidence of CLS.
- ✓ The incidence of CLS by various kinds of **anti-CD25 was 36.7%** by overall estimation and 42.2% by meta-analysis.



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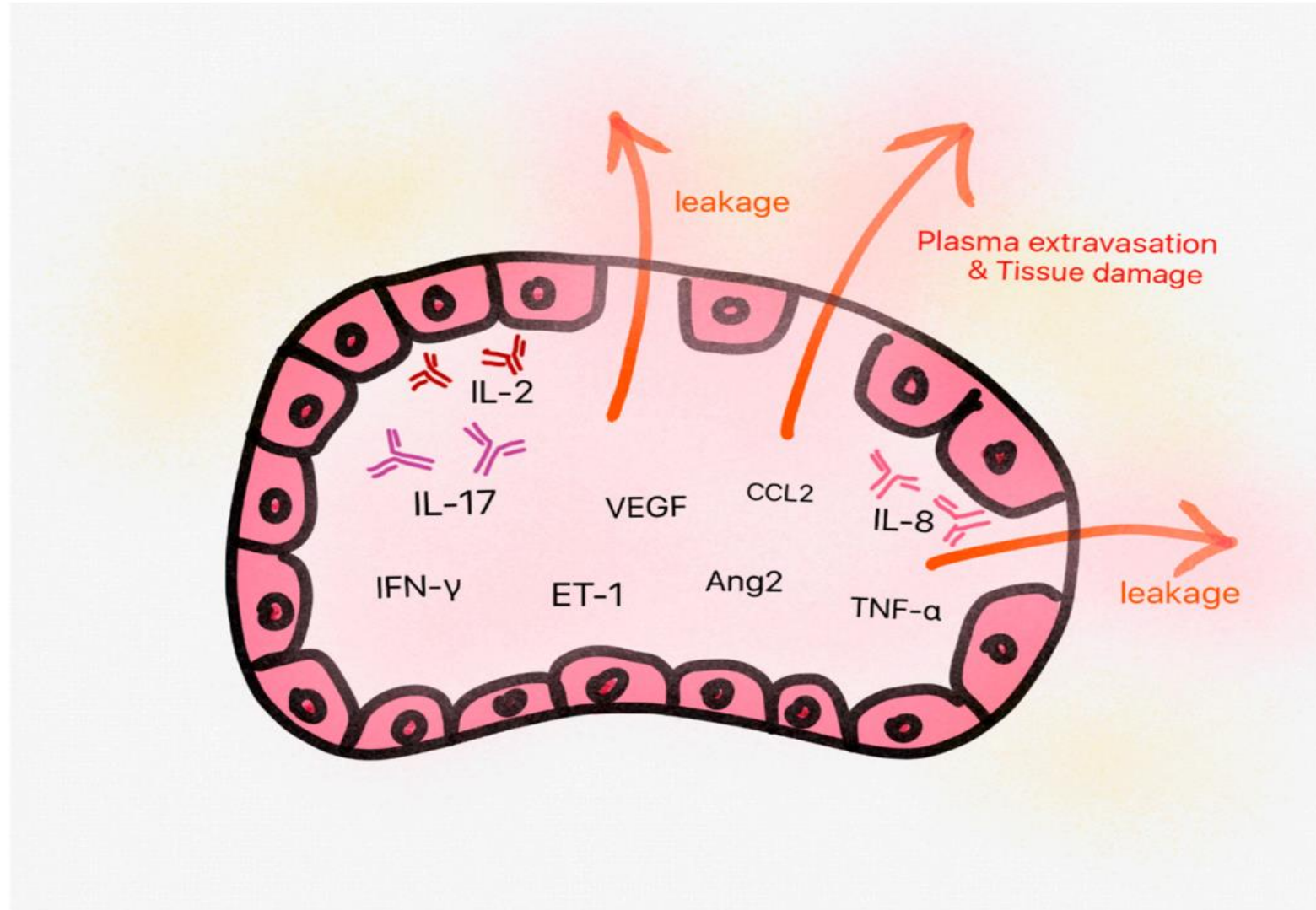
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- ✓ Multiple animal studies suggest that IL-2 causes the **acute injury of normal tissues** by
- ✓ enhancing **neutrophil adhesion**
- ✓ generating **reactive oxygen intermediates**
- ✓ **proteases**
- ✓ **pro-inflammatory cytokines** such as **TNF alpha**, which can cause vascular leakage.



## The proposed pathogenesis of capillary leak syndrome (CLS).



- ✓ We also found that **BMT** may be an important risk factor for CLS in cancer patients.
- ✓ The **incidence** of CLS associated with BMT with or without other agents ranged from **6.8% to 52.7%**.
- ✓ The pathophysiology of CLS in BMT-related CLS has not been fully studied.
- ✓ Some hypotheses on the contributing factors have been suggested such as pivotal contribution by **circulating leukocytes, decreased C1 esterase inhibitor activity, elevated C4d concentrations**, the use of **G-CSF or GM-CSF**, and elevation of **terminal complement complex (TCC)** levels.



- ✓ However, these studies did not report on the treatment strategies or clinical outcome of CLS, because most studies reported CLS as an adverse event of the drug.





## Nature Public Health Emergency Collection

Public Health Emergency COVID-19 Initiative

Memo. 2022; 15(2): 143–148.

PMCID: PMC8785001

Published online 2022 Jan 21. doi: [10.1007/s12254-021-00789-z](https://doi.org/10.1007/s12254-021-00789-z)

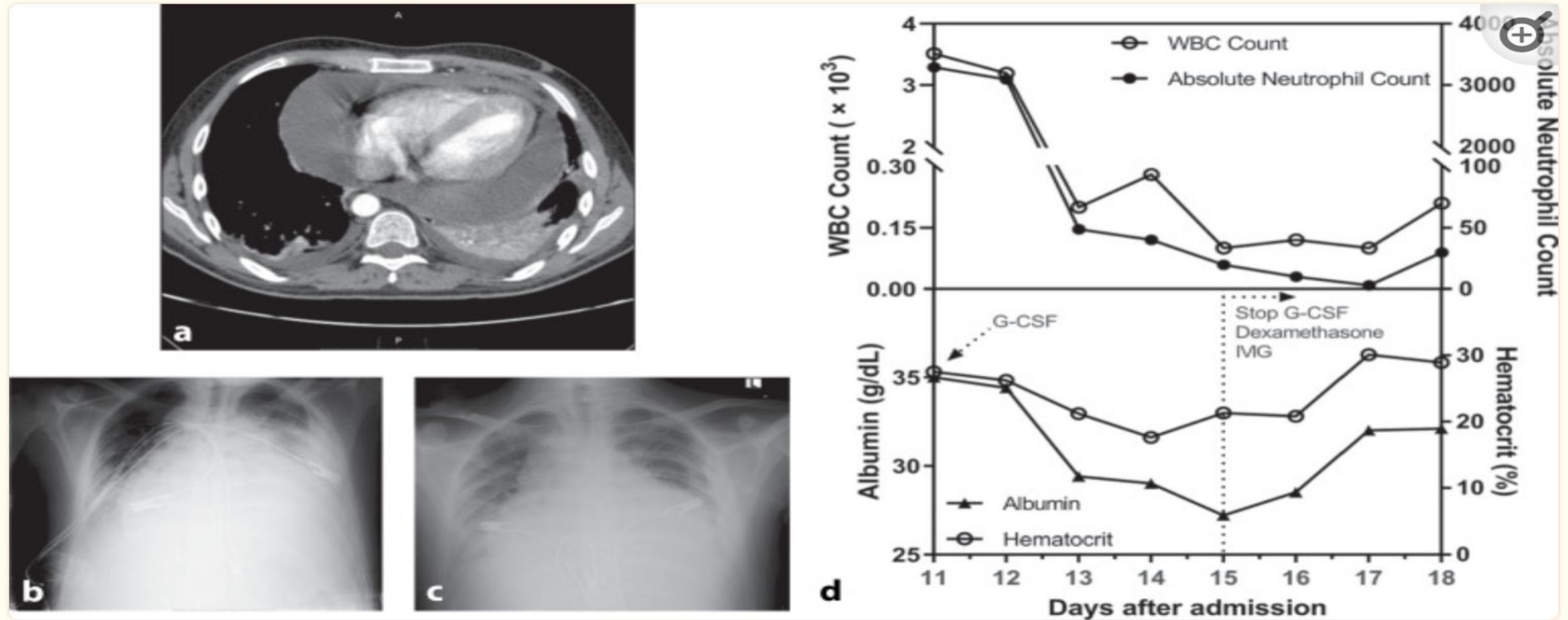
PMID: [35096191](https://pubmed.ncbi.nlm.nih.gov/35096191/)

### Systemic capillary leak syndrome following granulocyte colony-stimulating factor therapy in a T-lymphoblastic leukemia/lymphoma patient: a case report

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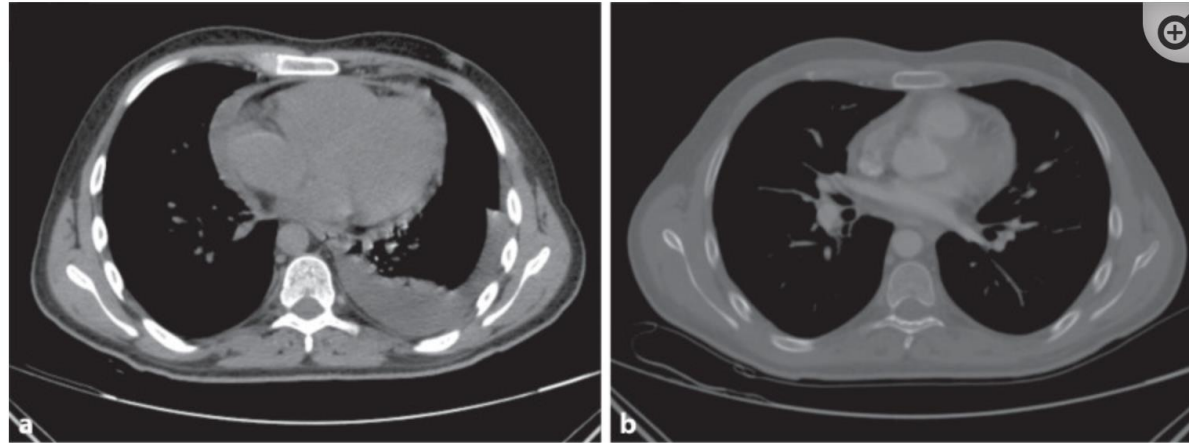
**Fig. 1**

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Computed tomography (CT) scan with intravenous (IV) contrast showed severe pericardial effusion with a maximum thickness of 4.5 cm with enhancing pericardium associated with bilateral pleural effusion more on the left side and bilateral atelectatic changes on day 13 (a). Chest X-ray on day 14 (b). Chest X-ray on day 15 several hours after dexamethasone and intravenous immunoglobulin (IVIg) therapy (c). A visual representation of daily changes in albumin, hematocrit, white blood cell (WBC) count and absolute neutrophil count during the systemic capillary leak syndrome (SCLS) attack and following therapy (d)



Fig. 2



Chest computed tomography (CT) scan on day 24 after admission showing significant improvement in the pericardial effusion with a maximum thickness of 1 cm. Left-sided pleural effusion with subsegmental collapse consolidation in the lower left lung (a). Follow-up chest CT 1 month after the previous scan revealed complete resolution of pericardial and pleural effusions with no atelectatic changes (b)



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[Rev Clin Esp \(Barc\)](#). 2022 June-July; 222(6): 374–376.

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Systemic capillary leak syndrome after SARS-CoV-2 infection and after COVID-19 vaccination: A scoping review in relation to a clinical case<sup>☆</sup>

Síndrome de fuga capilar sistémica tras infección por SARS-CoV-2 y tras vacunación contra COVID-19: una revisión de alcance a propósito de un caso

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نفروتوکسین‌ها و کلیه

Kidney and Nephrotoxins

۱۳-۱۵ مهر ۱۴۰۱-تهران

Characteristics of systemic capillary leak syndrome (SCLS) in cases (with SARS-CoV-2 infection or COVID-19 vaccination) described in the literature.

Article	Patient			Monoclonal gammopathy	Triggering factor	Laboratory test		
	Age	Sex	Prior SCLS			Hemoglobin (g/dL)	Albumin (g/dL)	Creatinine (mg/dL)
Our study (2021)	38	M	No	IgG kappa IgA kappa	SARS-CoV-2 PCR +	23.6	1.7	3.8
Beber et al. (2021) <a href="#">4</a>	55	W	No	NI	SARS-CoV-2 PCR +	21	3.5	1.4
Cheung et al. (2021) <a href="#">5</a>	59	W	No	NI	SARS-CoV-2 PCR +	17.1	2.4	NI
	36	M	Yes	IgG lambda	SARS-CoV-2 PCR +	>25	NI	NI
Case et al. (2020) <a href="#">6</a>	63	M	No	NI	SARS-CoV-2 PCR +	21.6	<1.5	2.35



[Vaccines \(Basel\)](#). 2022 Jun; 10(6): 835.

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PMCID: PMC9227463

PMID: [35746443](https://pubmed.ncbi.nlm.nih.gov/35746443/)

## A Disproportionality Analysis for Association of Systemic Capillary Leak Syndrome with COVID-19 Vaccination Using the World Health Organization Pharmacovigilance Database

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Silvio Tafuri, Academic Editor



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- ✓ Among the overall ADR reports for COVID-19 vaccines, we identified 101 cases (0.004%) of SCLS.
- ✓ Among these ADR-reported cases for SCLS,
  - ✓ 48 were from BNT162b2, 12 from mRNA-1273, and 41 from ChAdOx1



Demographics and characteristics of reported cases with systemic capillary leak syndrome (SCLS) according to type of COVID-19 vaccines.

Characteristics	Total (n = 101)	BNT162b2 (n = 48)	mRNA-1273 (n = 12)	ChAdOx1 nCoV-19 (n = 41)
Age, years				
≤11	0 (0)	0 (0)	0 (0)	0 (0)
12-17	1 (1)	1 (2)	0 (0)	0 (0)
18-44	13 (13)	9 (19)	1 (8)	3 (7)
45-64	36 (36)	9 (19)	11 (92)	16 (39)
65-74	19 (19)	7 (15)	0 (0)	12 (29)
≥75	7 (7)	3 (6)	0 (0)	4 (10)
Unknown	25 (25)	19 (40)	0 (0)	6 (15)



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Outcome				
Recovered	24 (24)	9 (19)	9 (75)	6 (15)
Recovered with sequelae	5 (5)	1 (2)	2 (17)	2 (5)
Recovering	19 (19)	11 (23)	0 (0)	8 (20)
Not recovered	17 (17)	5 (10)	1 (8)	11 (27)
Death	5 (5)	2 (4)	0 (0)	3 (7)
Unknown	31 (31)	20 (42)	0 (0)	11 (27)



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- ✓ In any case, it becomes clear that this condition is **underreported** due to the fact that it is **commonly misdiagnosed** owing to its resemblance in signs and symptoms with other prevalent conditions including **sepsis, angioedema, and anaphylaxis**, as well as its nonspecific signs and symptoms, not to mention the high mortality rates

