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重症COVID-19患者凝血功能异常所致血栓形成的研究进展

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摘 要

2019年12月左右，新型冠状病毒肺炎出现，这场新冠肺炎疫情传染性极强、传播速度极快，成为全球重大公共卫生事件，危及着全人类的健康。世界各国卫生组织竭尽全力抗击着这场疫情战役，虽然通过提高病例检测能力、社会防御意识和促进疫苗注射等因素可能在很大程度上对疫情进行了有效防控，但全球多个国家依旧已经或正在经历着多次暴发。绝大部分患者是可以痊愈的，但仍有部分患者转化为重症或危重症，严重者甚至死亡。对于重症新型冠状病毒肺炎患者，除了呼吸衰竭外，凝血功能异常引起的相关临床并发症也是使患者病情突然恶化，甚至死亡的重要原因之一。根据ISTH发布的弥散性血管内凝血病(DIC)标准，一些重度COVID-19感染患者可发生凝血功能障碍，并伴有爆发性凝血激活，导致广泛的微血管血栓形成和凝血因子消耗。已有研究结果显示，凝血功能异常与COVID-19患者的病重率和死亡率密切相关。本文通过对COVID-19患者中凝血功能异常和其发生的相关机制、治疗策略等方面进行综述，以便为COVID-19及之后可能出现的类似疾病的治疗提供参考方案。

关键词

新型冠状病毒，重型，凝血功能异常，血栓形成，治疗

Research Progress on Thrombosis Caused by Coagulation Disorders in Severe COVID-19 Patients

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Abstract

In December 2019, a new type of Coronavirus pneumonia emerged, the epidemic is highly infectious, spread very fast, the crowd has a universal susceptibility to become a major global public health event, endangering the health of all mankind. Health organizations around the world are doing their best to fight the epidemic, although by improving case-detection capabilities, factors such as social defense awareness and self-protection ability, promotion of vaccination and herd immunity may have effectively prevented and controlled the epidemic to a large extent, but many countries around the world have still experienced or are experiencing multiple outbreaks. The vast majority of patients can be cured, but there are still some patients may be transformed into severe or critical illness, serious or even death. For severe Coronavirus pneumonia, in addition to respiratory failure, coagulation disorders caused by clinical complications is also a sudden deterioration of the disease, even one of the important causes of death. According to the disseminated intravascular coagulation (DIC) criteria issued by ISTH, some patients with severe COVID-19 infection can develop coagulation dysfunction with explosive coagulation activation, resulting in extensive microvascular thrombosis and coagulation factor depletion. Previous studies have shown that the coagulation disorders is closely related to the serious illness rate and death rate of patients with COVID-19. In this review, the mechanism and treatment strategies of coagulation disorders in COVID-19 patients were reviewed in order to provide reference for the treatment of COVID-19 and similar diseases.

Keywords

COVID-19, Severe, Coagulation Disorders, Thrombosis, Treatment

1. 新型冠状病毒肺炎的简介

2019 年 12 月，出现了多起原因不明的肺炎病例，通过相关病毒分型检测，发现这是一种由新型冠状病毒(SARS-CoV-2)感染引起的急性、传染性极强的呼吸系统疾病，并于 2020 年 1 月 12 日，由世界卫生组织(WHO)正式命名为 2019 新型冠状病毒(COVID-19)。COVID-19 是一种包膜为β属的新型冠状病毒，该新型冠状病毒的基因组是由包裹在包膜里的单股正链 RNA 组成[1]，研究表明，刺突蛋白(S)、包膜蛋白(E)、膜蛋白(M)、核壳蛋白(N)为 SARS-CoV-2 的四种主要结构蛋白，而刺突蛋白(S)在病毒感染宿主细胞及致病过程中发挥着极为重要的作用，特别是，刺突表面单位(S1)与血管紧张素转换酶 2 (ACE2)细胞受体具有高度亲和力[2]，且 ACE2 在肺泡上皮细胞、动脉内皮细胞、小肠上皮细胞和免疫组织中高度表达，这有助于病毒粒子对接到靶细胞表面，使新型冠状病毒更容易侵入到宿主细胞中[3]，从而导致组织受损甚至多器官衰竭。相关研究表明感染 COVID-19 后，大部分患者预后良好，而重症患者多见于老年人。因此，老年人群更应该是值得被重点关注的人群。

2. COVID-19 相关凝血病的临床特征

目前，新型冠状病毒相关凝血病被认为分为 3 个阶段：第一阶段：D-二聚体升高；第二阶段：D-二

聚体升高伴轻度凝血酶原时间(PT)/国际标准化比值(INR)和活化部分凝血活酶时间(APTT)以及轻度血小板减少；第三阶段：为危重疾病，向经典弥漫性血管内凝血(DIC)进展。

2.1. COVID-19 相关的静脉血栓栓塞风险

在大流行早期，就有相关研究证实了重症 SARS-CoV-2 感染者发生静脉血栓栓塞的风险在不断增加。在最早的一份报告中，Cui 等人[4]回顾性评估了在中国一家医疗机构住院的 81 例重症 COVID-19 患者，并报告了有 25% (20/81)的重症监护病房(ICU)患者发生了 VTE。在这项研究中，对患者没有使用预防性抗凝剂。荷兰的一份早期报告显示，尽管使用了药物预防 VTE，但入住 ICU 的重症 COVID-19 患者的 VTE 发生率为仍为 27% [5]。法国一个研究小组最近的一项分析显示，尽管接受了抗凝治疗，但 150 例 COVID-19 ARDS 患者的血栓栓塞并发症发生率(11.7%)远高于非 COVID-19 ARDS 患者的历史对照组(2.1%) [6]。法国另一个研究小组也发现 PE 患病率为 20.6%，高于前一年同期 ICU 患者队列的 6.1% [6]。在首批 107 例入住 ICU 的患者中，有 22 例发生 PE，其中 20 例发生在标准剂量 VTE 预防治疗期间[7]。早期尸检报告显示微血管血栓形成和明显的炎症改变，进一步证实了 COVID-19 相关的静脉血栓栓塞风险[8]。因此，有必要在早期识别血栓事件风险的增加，并尽可能预防血栓事件和器官损伤。

2.2. COVID-19 相关的异常凝血指标

虽然 COVID-19 对所有的凝血指标都可能存在影响，但是其与疾病的严重程度及死亡率的相关性存在着明显差异[9]。多项研究表明，在 COVID-19 重症患者中，D-二聚体是显示 COVID-19 疾病严重程度和死亡率的有效生物标志物。由于 D-二聚体只在交联纤维蛋白降解时产生，因此 D-二聚体可作为机体凝血活化和继发纤溶激活的标志物[10]。因此 D-二聚体水平的升高与全身的高凝状态和血栓栓塞形成具有高度相关性。在多数 COVID-19 患者中，血小板计数通常正常或轻度降低，但严重的血小板减少症与疾病进展有关，会使发生严重疾病甚至死亡的风险率增加 5 倍以上[11]。与传统脓毒症相比，大多数 COVID-19 患者的 APTT 和 PT 正常或者轻度延长，极少有患者的纤维蛋白原降低。在 COVID-19 患者中 APTT 和 PT 延长的概率分别为 6%和 5% [12]。D-二聚体是诊断和预测 VTE 复发的有效指标，它是 DIC 的早期敏感标志物[13]，与轻症患者相比，重度及危重症患者的 D-二聚体水平较高(平均水平为 2.4 mg/L vs 0.5 mg/L)，且与存活率呈负相关[14]。因此，D-二聚体不仅在重症 COVID-19 中具有高度的预后性，更是与病情的严重程度和死亡率呈相关性[15]。

3. COVID-19 相关凝血病的发生机制

COVID-19 凝血功能障碍的机制很复杂。它包括内皮细胞的直接损伤、炎症反应的失衡、免疫系统的过度激活等[16]。SARS-CoV-2 与血管紧张素转换酶 2 (ACE2)的亲和力是 SARS 的 10~20 倍[17]。ACE2 在肺泡上皮细胞、动脉内皮细胞、小肠上皮细胞和免疫组织中表达[18]。此外，SARS-CoV-2 的感染使免疫系统过度激活，导致不受控制的炎症损伤[19]。当炎症－凝血相互作用压倒自然防御系统时，就会发生灾难性事件并导致恶性循环。

3.1. COVID-19 感染患者的内皮细胞损伤

内皮细胞在调节止血、纤维蛋白溶解和血管壁通透性方面具有重要作用，肺微血管中的内皮功能损伤是静脉血栓形成的触发因素，内皮功能障碍被认为是冠状病毒感染的重要病理生理事件，可以直接感染血管内皮细胞，导致细胞损伤凋亡，从而降低正常内皮细胞的抗血栓活性[20]。肺泡损伤、血管壁水肿、透明血栓和外周小血管弥漫性血栓已成为 COVID-19 所致呼吸衰竭的主要病理特征[21]。内皮细胞损伤是微血栓形成的主要危险因素之一，研究发现，重症 COVID-19 破坏内皮细胞后易导致急性肺损伤、心源

性损伤和肾损伤[22]。病毒对位于肺泡和小气道上皮细胞的病变作用也支持内皮细胞损伤的存在，其特征是内皮肿胀以及肺毛细血管中聚集的巨核细胞[23]。因此，病毒包涵结构和 mRNA 表达进一步支持 SARS-CoV-2 进入内皮细胞。

此外，炎症环境触发活化组织因子在内皮细胞、巨噬细胞和中性粒细胞上的表达，从而放大肺内凝血级联反应的激活[24]。其中过度炎症触发了高凝状态，重症 COVID-19 患者微血管内的血小板活化增加易发生血栓形成。内皮细胞受损与患者的不良预后相关[25]，由表面受体(整合素和选择素)和粘附蛋白(VWF 和纤维蛋白原)介导的血小板－血管壁相互作用会损害血管壁完整性，最终导致微血管阻塞[26]。此外，血小板在 COVID-19 患者中过度活化，可通过中性粒细胞加重血栓炎性级联反应[27]，这是免疫血栓形成的基本要素。所有这些因素都支持内皮功能障碍和血小板活化是 COVID-19 相关凝血功能障碍的关键特征，并可能导致多器官功能损伤。

在 COVID-19 的急性期，除了介导炎症免疫应答外，SARS-CoV-2 还可以通过与 AEC2 结合直接损伤 EC [28]。EC 损伤会导致内皮活化、屏障功能丧失和通透性增加，随后导致微血管渗漏[29]。内皮损伤可诱发弥漫性和全身性内皮功能障碍，并激活多种免疫介导的炎症通路和血栓形成，从而导致严重的多器官受累和随后的死亡率增加[30]。在一部分恢复期患者中观察到内皮病变和凝血标志物也会升高，表明感染可能诱发慢性凝血病、内皮炎和微血管病变，并伴有微血栓形成[31]。这进一步表明，内皮损伤会使组织因子和胶原暴露于血液中，启动凝血级联反应。

3.2. 血小板活化

血小板是机体极为重要的免疫细胞，除了在病理、生理中发挥着重要的止血功能外，在抗病毒免疫的过程中也起着一定作用。研究报道，血小板减少症可能会增加 COVID-19 患者住院期间严重出血或院内死亡并发症的风险，因此应作为住院期间病情恶化的指标[32]。最近数据表明，由 COVID-19 引起的凝血障碍可能与常见感染诱发的 DIC 不同。循环生物标志物的增加可能直接与血小板受体结合，随后血小板过度激活和聚集，在这种过度激活期间，血小板计数较低[33]。血小板不仅直接参与 COVID-19 患者高凝状态的形成，同时还参与全身炎症反应，通过释放炎症介质并与其他免疫细胞相互作用的反应形成细胞因子风暴，进一步促进高凝状态及血栓形成[34]。据推测，SARS-CoV-2 通过特异性受体抑制骨髓造血，由此抑制了 PLT 的形成导致血小板减少症[35]。病毒感染和炎症反应导致肺毛细血管损伤，受损的肺组织和肺内皮细胞可能导致巨核细胞破裂和 PLT 消耗增加的过程[36]。此外，SARS-CoV-2 可以增强自身抗体和免疫复合物形成，加重了免疫系统对 PLT 的特异性破坏[37]。PLT-白细胞聚集体和 PLT-内皮相互作用似乎在急性肺损伤的发病机制中起作用[38]。在 COVID-19 感染中，肺组织和肺内皮细胞的损伤可引起 PLT 聚集，形成微血栓并进一步消耗 PLT [39]。

3.3. NETs 水平的升高

内皮细胞的损伤还可以激活一种称为中性粒细胞胞外陷阱(NET)的主要防御机制。NET 由于染色质解凝而释放，然后立即扩散[40]。对于 NET 诱导的血栓形成，已经提出了几种途径。首先，血小板和内皮释放的 VWF 与 NET 相互作用并导致血小板粘附和纤维蛋白形成。其次，存在于 NETs 中的组蛋白被认为是强大的损伤因子可以通过激活血小板上的 TOLL 样受体引起血小板聚集。第三，中性粒细胞释放一种丝氨酸蛋白酶，即弹性蛋白酶，它可以通过降解血小板调节素和组织因子通路抑制剂来阻止纤维蛋白溶解系统[41]。其次，NET 是由 NLRP3 炎症小体和促炎细胞因子刺激 NADPH 氧化酶后产生的氧化应激。一旦释放，包括与颗粒和细胞质中的杀菌蛋白相关的染色质的 NET 成分会进一步增强促炎反应[42]。虽然 NET 主要具有抗菌功能，但过量可引起细胞炎症和组织损伤，增加内皮层的血栓形成。事实上，NET

通过诱发外源性和内源性凝血通路，在各种来源的凝血和血栓形成的发病机制中发挥着积极作用[43]。在重症 COVID-19 中，NET 的形成与 ARDS 和高凝状态有关，是疾病严重程度的预测因子。

3.4. 细胞因子风暴

当病毒侵入机体时，机体的防御系统会发挥作用，以此来保护机体不受伤害，然而，当自身免疫系统过度激活时，则会导致大量细胞因子的分泌，当细胞和病毒之间存在相互作用时细胞因子风暴被激活，以此促进炎症环境，最终导致血栓形成[44]。细胞因子信号转导、缺氧、组织损伤和 DAMP 会触发 EC 从抗凝剂转变为促凝血剂表型。炎症和凝血级联反应形成复杂的网络[45]，炎症是免疫系统对损伤或感染做出反应而触发的一种防御机制，其特征是局部血流量增加、白细胞募集以及细胞因子和趋化因子的释放，可促进病原体清除[46] [47]。炎症还会诱导内皮细胞上粘附分子的表达增加，随后白细胞和内皮细胞(EC)之间的相互作用可导致免疫细胞激活，在炎症条件下，中性粒细胞和血小板之间的相互作用、血小板活化、单核细胞组织因子表达、微粒释放、磷脂酰丝氨酸(PS)外化以及补体活化共同参与血栓形成[48]。炎症导致血细胞活化和凋亡，导致微粒释放和 PS 在血细胞和微粒上外化，显著提高肌腱酶和凝血酶原酶复合物的催化效率，促进凝血酶介导的纤维蛋白生成和局部血凝块形成，从而在损伤区域形成免疫血栓形成。

3.5. 补体的激活

补体系统作为先天免疫反应的一个组成部分，也参与内皮细胞的活化，并有助于在炎症和血栓形成之间形成正反馈回路。该系统的主要活性是建立多蛋白膜攻击复合物(MAC)，该复合物通过渗透裂解或巨噬细胞介导的吞噬作用导致病原体死亡。宿主免疫系统在与激活补体系统的病原体相互作用时做出反应。然而，补体系统不受控制的激活导致急性和慢性炎症、血管内凝血、细胞损伤，进一步导致多器官功能衰竭[49]。有 30 种蛋白质参与补体系统的 3 种活性途径。这三种途径包括经典途径、凝集素途径和替代途径。病毒激活的凝集素通路导致高水平的炎症反应以及病毒感染[50]。SARS-CoV-2 通过经典通路和凝集素通路激活补体级联反应[51]。补体系统是炎症和血栓形成的主要因素。C3a 和 C5a 募集并激活中性粒细胞和单核细胞以释放促炎细胞因子(IL-6、IL-8)。C5a 可以上调中性粒细胞和 EC 上 TF 的表达，进而发挥促凝血作用[52]。C5a 还可以通过增加肥大细胞和嗜碱性粒细胞中纤溶酶原激活剂抑制剂 1 (PAI-1)的释放来抑制纤维蛋白溶解[53]。与天然抗体和诱导抗体的免疫应答相关的病毒抗原产生 C1 水平，并通过经典途径启动补体系统的激活[54]。在慢性心力衰竭中也观察到补体激活与内皮激活之间的相关性，这表明这两个系统在血管疾病中具有相互关联的意义。

4. COVID-19 相关血栓的治疗

重度 COVID-19 患者常处于高凝状态，发生血栓栓塞的风险率较高，是患者病情突然恶化甚至死亡的主要原因之一，因此，抗血栓治疗已成为 COVID-19 标准治疗中的一部分。

4.1. 抗凝治疗

因为 D-二聚体水平升高提高了患者的死亡率，因此，如果没有禁忌证，所有的 COVID-19 住院患者都应该考虑抗凝治疗[55]。包括使用普通肝素、低分子肝素(LMWH)、依诺肝素、华法林、利伐沙班等其他抗凝药物。在一项研究中，招募了 449 名 COVID-19 重症患者，其中 99 名接受了至少 7 天的 LMWH 治疗，显著降低了住院患者的死亡率[56]。研究发现，LMWH 对脓毒症诱导的凝血病评分高(≥4)或 D-二聚体水平显著升高(>6 倍)的患者有益[57]，明显降低了死亡率。

研究表明，肝素可降低疾病严重程度和死亡的风险[58] [59]。肝素或低分子量肝素除具有抗凝血特性

外，还具有额外的抗炎和抗病毒作用[60]。肝素属于糖胺聚糖家族，其聚阴离子性质允许与其他结构结合，例如抗凝血酶、细胞因子、趋化因子、细胞毒肽和参与炎症的补体蛋白。此外，肝素还可以降低 P-选择素的表达，导致白细胞与内皮细胞的粘附减少[61]。LMWH 的一些非抗凝特性包括与炎性细胞因子结合、抑制中性粒细胞趋化性和白细胞迁移、中和带正电荷的补体因子 C5a 以及抗病毒作用[62]，减少胶原沉积和抗心律失常作用，调节内皮功能障碍，改善微血管功能障碍和缓解肺凝血功能障碍[63]。尽管对 COVID-19 患者进行了充分的血栓预防，但仍有 4.4%的患者出现症状性 VTE，2.5%的患者出现缺血性脑卒中，1.1%的患者出现心肌梗死。血栓性并发症的总体患病率从非危重症患者的 2.6%到危重症患者的 35.3%不等[64]。这意味着单独使用肝素或当前剂量是不够的，需要其他抗凝剂和/或其他伴随疗法来解决 COVID-19 中的高凝状态。相关试验表明，治疗剂量的抗凝对 COVID-19 重症患者没有益处，甚至可能会造成伤害。随着冠状病毒新变异株的出现，抗凝治疗对 COVID-19 重症患者的益处和风险可能会发生变化[65]。总而言之，目前的临床证据表明重症 COVID-19 患者的抗凝治疗应被高度重视。

4.2. 抗血小板治疗

抗血小板药物通过拮抗 $P2Y_{12}$ 受体(氯吡格雷、普拉格雷)、抑制磷酸二酯酶(双嘧达莫)或抑制环氧合酶-1 (COX-1) (阿司匹林)起作用，所有这些都是血小板活化和聚集的关键途径[66]。COX-1 的激活导致血栓素 A_2 的产生和血小板反应性增加。阿司匹林通过抑制 COX-1 不可逆地抑制血小板功能。同样，$P2Y_{12}$ 受体使糖蛋白 IIb/IIIa 受体激活，导致血小板脱颗粒、血栓素 A_2 产生和血小板聚集[67]。血小板聚集是血栓形成的促成因素之一，有研究发现抗血小板药物双嘧达莫在体外可抑制新冠病毒的复制；在使用双嘧达莫治疗 COVID-19 时，还发现其能显著改善血小板和淋巴细胞计数，降低 D-二聚体水平。抗血小板药物双嘧达莫除了抗血小板功能外，该药物还具有广谱抗病毒活性(特别是针对正链 RNA 病毒)，抑制炎症并促进粘膜愈合，同时还能预防肺、心脏和肾脏的急性损伤和纤维化[68]。COVID-19 患者的双嘧达莫治疗也能通过促进中性粒细胞中 3’,5’-环磷酸腺苷(cAMP)产生来预防 NETosis 的额外益处，有研究证明，双嘧达莫可以通过 I 型干扰素反应在体外抑制 SARS-CoV-2 复制，使重症 COVID-19 患者的临床状态有所改善[69]。

4.3. 靶向 NETs

由于 NETs 在 COVID-19 的血栓形成过程中具有重要作用，针对 NETs 的一些药物也在临床中使用或不断开发中，例如 Sivelestat，Sivelestat 是一种竞争性、可逆性和选择性的中性粒细胞弹性蛋白酶(NEase)抑制剂，不影响其他细胞蛋白酶的活性[70]。相关临床研究表明，sivelestat 通过调节肺血管通透性、病原体清除和中性粒细胞介导的肺上皮损伤而有效对抗 ARDS [71]。sivelestat 不仅可以改善全身炎症综合征和 ARDS 患者的肺功能、缩短机械通气持续时间和血氧饱和度。还可以联合重组人可溶性血栓调节蛋白有效减轻重症监护病房(ICU)患者弥散性血管内凝血病引起的 ARDS，提高生存率和无呼吸机时间[72]。因此，sivelestat 可能是一种很有前途的疗法，通过抑制 NEase 和 NET 的形成来控制 COVID-19 诱导的急性肺损伤、ARDS 和凝血功能障碍[73]。

4.4. 细胞因子抑制剂

细胞因子风暴在 COVID-19 的发病机制中发挥着关键作用，对 COVID-19 的病情进展及血栓形成有着不可替代的作用。因此，我们可以通过抑制炎症因子从而延缓疾病的进展。而 IL-6 在炎症细胞因子中占有较多比例，其中，托珠单抗是一种靶向 IL-6RA 的人源化单克隆抗体，是一种免疫抑制药物[74]，在住院的 COVID-19 患者中，使用 IL-6 受体拮抗剂(IL-6RA)治疗可降低患者死亡率。IL-6RA 最明显的受益

者是接受呼吸支持的 COVID-19 患者，包括无创通气和有创机械通气[75]。托珠单抗已被证明可以降低 COVID-19 患者的炎症水平并改善症状和预后。

4.5. 补体抑制剂

补体的激活是导致 COVID-19 患者血栓形成的原因之一，因此我们可以通过使用补体抑制剂来减少血栓事件的发生。目前，经食物药品监督管理局(FDA)批准的补体抑制剂有两种(依库珠单抗和拉武珠单抗)，它们都与 C5 结合，并在空间上阻断 C5 向 C5a 的裂解，从而形成膜攻击复合物[76]。有研究证实，与单独接受标准治疗的患者相比，经依库珠单抗治疗后改善了患者 15 天生存率和缺氧症状[77]。C3 抑制剂阻断了细胞因子失调和 NET 的产生，对 COVID-19 重症患者免疫血栓形成的治疗产生更为有益的效果[78]。但事实上，在临床使用补体抑制剂来治疗 COVID-19 的病例较少，我们仍需要更多的临床试验来取得进一步的研究进展。

5. 结语

COVID-19 大流行为全社会带来了前所未有的挑战，尽管这种传染病的死亡率似乎不高，但重症患者仍具有发生急性呼吸窘迫综合征和不良临床结果的高风险。COVID-19 不仅仅是呼吸系统疾病，更是一种累及多系统病变的综合征，是一种与凝血功能障碍有关的全身性疾病。本文通过对 COVID-19 血栓形成相关机制及抗凝治疗的描述，希望提高广大医务工作者对相关疾病的认知，做到早发现、早诊断、早治疗。虽然，经过抗凝治疗后血栓患者的发病率有一定程度的降低，但部分患者仍存在一定的血栓发生率，因此，需要我们建立更完善的 COVID-19 患者预防血栓的有效动态监测及治疗体系，提高临床治疗的有效性和安全性。

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