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# 红细胞与骨创伤患者深静脉血栓形成研究进展

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## 摘　要

**红细胞一直被视为血栓形成的旁观者，然而越来越多的临床和实验室证据表明红细胞在血栓形成和止血过程中扮演着积极角色。本综述对骨创伤患者深静脉血栓形成中红细胞的作用进行了全面综合分析。临床和流行病学研究已经证实，红细胞相关指标异常，如血细胞比容、红细胞分布宽度和红细胞平均体积变化等，在血栓性疾病的发生和预测方面具有较高的价值。骨创伤患者术前贫血的发生率相当高，且可能导致大量失血，从而增加围手术期输注红细胞的风险。在贫血患者和接受红细胞输注的患者中，红细胞异常与深静脉血栓形成密切相关。通过对血液流变学、凝血过程以及内皮细胞、血小板、纤维蛋白原和中性粒细胞等因素的影响，红细胞可以促进深静脉血栓生成。**

## 关键词

**红细胞，深静脉血栓形成，骨创伤**

# The Research Advancements in Deep Vein Thrombosis among Patients with Erythrocyte and Bone Trauma

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## Abstract

**Red blood cells have traditionally been considered as passive bystanders in thrombosis, however, there is mounting clinical and laboratory evidence indicating an active role of red blood cells in the**

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**processes of thrombosis and hemostasis. This comprehensive review thoroughly examines the involvement of red blood cells in deep vein thrombosis among patients with bone trauma. Clinical and epidemiological studies have substantiated that abnormal erythrocyte-related indicators, such as hematocrit, erythrocyte distribution width, and mean erythrocyte volume alteration, hold significant predictive value for the occurrence of thrombotic diseases. The incidence of preoperative anemia is notably high among patients with bone trauma, which can result in substantial blood loss thereby elevating the risk for perioperative red blood cell transfusions. Remarkably, red blood cell abnormalities exhibit a strong association with deep vein thrombosis not only in individuals with anemia but also in those who undergo red blood cell transfusions. By exerting influence on hemorheology, coagulation process, endothelial cells, platelets fibrinogen levels, and neutrophils activity, erythrocytes actively contribute to the promotion of deep vein thrombosis.**

## Keywords

**Red Blood Cells, Deep Vein Thrombosis, Bone Trauma**



## 1. 引言

静脉血栓栓塞症(venous thrombosis, VTE)包括深静脉血栓形成(DVT)和肺栓塞(PE)，是第三大最常见的心血管疾病，影响高达 5%的人口[1]。年龄较大、病程长、术中固定、使用全身麻醉、输血以及骨水泥等因素，以不同程度影响着血管内皮和血流，扰乱了凝血和纤溶系统的平衡，并促进了在骨创伤患者围手术期形成 DVT 的过程[2] [3]。因此，骨创伤患者是 DVT 发生的极高危人群。据报道，骨创伤患者围术期 DVT 发生率为 23%~28% [4] [5]。

红细胞一直被视为血栓形成的旁观者，然而越来越多的临床和实验室证据表明红细胞在血栓形成和止血过程中扮演着积极角色。血细胞比容升高(如真性红细胞增多症)或存在遗传性红细胞异常(如遗传性球形红细胞增多症、$\beta$-地中海贫血、镰状细胞性贫血)的患者更容易发生血栓形成[6] [7]。在此，我们简要回顾了红细胞相关指标异常与血栓形成之间的临床关联，贫血和输血与 DVT 形成的关系，以及红细胞与血栓形成的可能机制。

## 2. 红细胞相关指标异常与 DVT 形成

### 2.1. 血细胞比容

血细胞比容(HCT)是全血中红细胞所占比例，它是决定血液粘度的主要因素之一，增加血细胞比容与增加血液粘度以及提高血小板粘附性密切相关。血细胞比容水平超出正常范围的受试者，例如患有原发性或继发性红细胞增多症的个体，易于发生静脉血栓形成[8]。Musallam 等人对 197,469 例接受大手术的成年患者进行了分析，结果显示在术后 30 天内，与无血细胞比容升高的患者相比，血细胞比容升高的患者发生深静脉血栓和肺栓塞的风险更高[9]。Braekkan 等人的研究结果显示，在调整年龄、体重指数和吸烟因素后，对于整个人群而言，每增加 5%的红细胞压积，总静脉血栓栓塞风险比为 1.25 (95% CI: 1.08~1.44)，而无明显诱因静脉血栓栓塞风险比为 1.37 (95% CI: 1.10~1.71) [10]。然而，Warny 等人的研究认为高血细胞比容与静脉血栓栓塞风险增加无关[11]。这可能是因为不同研究中纳入个体数量存在差

异、高血细胞比容参考范围选择有所不同以及对血栓定义存在差异。因此，在评估 DVT 的风险时，应考虑血细胞比容。

### 2.2. 红细胞分布宽度

红细胞分布宽度(RDW)是血常规中一项用于评估循环红细胞体积异质性程度的重要指标，最初该参数被应用于贫血的诊断和鉴别。Bucciarelli 等人对 730 例 VTE 患者和 352 例对照组患者进行了研究，结果显示，在校正年龄、性别、体重指数、其他血液学变量和肾功能之后，相比于 RDW≤ 第 90 百分位的个体，RDW 超过第 90 百分位的个体 VTE 风险增加了 2.5 倍(OR: 2.52, 95% CI: 1.42~4.47)，这一发现证实了高 RDW 与 VTE 风险之间的关联，并提示了将 RDW 作为一种廉价且方便获得的标记物来进行 VTE 风险分层的可能性[12]。Xiong 等人对 2059 名接受全关节置换术(TJA)的病人进行多变量二元回归分析，发现 RDW-CV ≥ 13.2%和 RDW-SD ≥ 44.6 fL 的 TJA 患者术前 DVT 的风险分别增加 1.54 (P = 0.038, 95% CI: 1.03~2.3)倍，1.98 (P = 0.001, 95% CI: 1.32~2.98)倍[13]。目前尚不清楚 RDW 值升高与静脉血栓形成之间的关联原因。已有一些病因假设提出，首先，RDW 值升高的病例常伴有轻度贫血。其次，神经激素轴可能对红细胞生成产生影响。此外，RDW 和深静脉血栓形成也被认为和炎症有一些关系，通过炎症标志物如 c 反应蛋白、白细胞介素 6、白细胞介素 8 和单核细胞趋化蛋白起作用[14]。综上所述，RDW 在血栓性疾病发生及预后预测方面具有显著价值，为临床医师评估血栓性疾病患者的病情和预后提供了一项重要工具，应予以充分重视和广泛推广。

### 2.3. 平均红细胞体积

平均红细胞体积(MCV)是衡量红细胞大小的指标，与血细胞比容成正相关。关于 MCV 与静脉血栓形成之间的关系，目前尚无统一定论。Tural、Braekkan SK 等人的研究未能发现 MCV 与静脉血栓形成之间存在关联[10] [15]。相反地，Rezende 等人发现高 MCV (大于 101.5 fL)与静脉血栓形成之间存在显著相关性[16]。在老年髋部骨折患者中，入院时的平均红细胞体积(MCV)与术前深静脉血栓形成(DVT)的发生率呈正相关关系(OR: 1.03; 95% CI: 1.01~1.05; P = 0.0013)，可以将 MCV 视为预测 DVT 风险的一个重要指标[17]。高 MCV 引发 DVT 的潜在生物学机制包括以下几个方面：(1) 当平均红细胞体积增加时，血细胞比容也会增加；提高的血细胞比容导致血小板边缘化增加，进一步促进了血小板与内皮细胞之间的相互作用，并最终推动了血栓形成[18]。(2) MCV 升高会增加血液粘度，并且粘度随着大血管中 MCV 的升高而呈指数增加，从而阻碍血流速度，进而促使血栓形成[19]。(3) 随着 MCV 的增加，红细胞的变形能力下降，红细胞膜的刚性增加[20]，从而使得红细胞在微血管系统中通过困难，并促进血小板向边缘运动，进而促使血栓形成。综上所述，MCV 可被视为 DVT 风险的预测因子。

## 3. 贫血与输血和骨创伤患者 DVT 形成

### 3.1. 贫血

骨创伤患者发生术前贫血的可能性较大，原发性关节置换术的患者术前贫血的发病率为 15%~17% [21]。Feng 等人研究显示，术前贫血是老年髋部骨折患者术前深静脉血栓栓塞的独立因素[22]，这可能与贫血导致 D-二聚体升高相关。个别贫血类型引发红细胞大小、形状和弹性的改变，进而降低红细胞的变形能力并增加其硬度，从而促进静脉血栓生成。镰状细胞病作为一种潜在的 VTE 危险因素备受关注。镰状细胞是一种杂合子载体状态，其导致血红蛋白形态扭曲。已有若干研究证实，镰状细胞病患者红细胞变形能力下降，聚集性增加以及血液粘度升高，这可能对微循环血流产生影响，并增加 VTE 的风险[23]。地中海贫血患者的红细胞在凝血酶生成过程中具有活化血小板的功能，导致其血液处于高度凝聚状态，

从而促进了血栓形成，尤其是在脾切除术后[24]。同样，对于遗传性球形红细胞增多症患者，脾切除术后VTE 的风险增加了 3.3 倍[25]。在这两种情况下，脾切除术可以通过减少异常红细胞的清除来促进血栓形成[24] [25]。阵发性夜间血红蛋白尿是一种以补体介导的红细胞溶血为特征的疾病，其患者最常见死亡原因为血栓形成和栓塞，约占已知死亡原因人数的 40%至 67% [26]。这些疾病中的血栓形成可能是多种因素引起的，包括红细胞功能障碍以及对其他血细胞和血管系统的影响。

### 3.2. 输血

围手术期红细胞输注在骨创伤患者中比较常见，单侧全膝关节置换术(TKA)患者的异体输血发生率为 3.5%~18.5%，单侧全髋关节置换术(THA)患者的发生率为 5.4%~26.2% [27]。输血可能通过以下机制促进血栓形成：首先，输血可改变局部血液流变学，增加血液粘度，从而导致红细胞聚集，并随之形成血栓。其次，输注储存的红细胞会刺激中性粒细胞释放炎症细胞因子，例如 IL-8 和 sPLA2 [28]，从而进一步增加血栓形成的风险。红细胞输注可能会引起血小板反应性增加[29]，这可能在血栓形成过程中发挥一定作用。此外，储存的红细胞释放游离血红蛋白和微泡，降低一氧化氮水平并导致血管收缩[30]。

根据目前有限的证据，关于骨创伤患者输血与术后深静脉血栓形成之间的关系仍存在争议。Jiang T 等人分析了 TKA 和 THA 的输血结果，发现围术期输血增加了术后深静脉血栓形成的风险[31]。然而，Frisch 等人在接受全关节置换术的患者中没有发现输血和深静脉血栓之间的关系[32]。此外，Spinella 等人进行了一项调查研究，探讨红细胞贮存时间与创伤患者深静脉血栓发生率之间是否存在关联，发现输注储存超过 28 天的红细胞明显增加了深静脉血栓形成(DVT)的风险[33]。随着储存时间的延长，红细胞发生形态学和生化变化，这被称为“血液储存病变”。在储存过程中，红细胞的变形能力降低，渗透脆性增加，并且会形成球形红细胞，这与细胞内 ATP 和 DPG 水平逐渐降低以及 pH 值下降相关[34]。此外，长期储存的红细胞有利于氧化应激条件，导致脂质过氧化、细胞膜和细胞骨架蛋白氧化以及红细胞膜完整性降低[35]，这些变化被视为促进血栓形成的因素。因此，在临床实践中，医生应仔细考虑红细胞输注的适应症，特别是对于存在 VTE 危险因素的患者。

## 4. 红细胞与 DVT 形成的可能机制

### 4.1. 血液流变学

红细胞能够通过多种变化对血液流变学产生影响，从而促进 VTE 的形成。(1) 血细胞比容增加：血液的粘度很大程度上取决于细胞成分的浓度(即血细胞比容)。血细胞比容增加会导致血液粘度增加，减少血流量，进而导致血栓形成[36]。此外，血细胞比容升高会促进血小板和凝血因子向血管壁的移动，从而增加血小板与血管内皮以及与血小板自身之间的碰撞[37]。(2) 红细胞聚集增加：在低剪切率或血液瘀滞的情况下，红细胞往往会形成线性排列的堆叠细胞 (roleaux)或三维聚合物[38]。这种聚集体难以分散，且常导致下肢静脉等较大低剪切力血管的血液粘度和流体动力学阻力增加。红细胞聚集有助于促进静脉血栓形成，从而证实了局部血液流变学改变在静脉血栓形成中的重要性。(3) 红细胞变形能力降低：变形能力是红细胞改变其几何结构以最大程度地降低流动阻力的能力。红细胞的变形性主要源于其双凹圆盘结构具有较高的表面积与体积比。红细胞僵硬度增加可能导致其无法顺利通过毛细血管，从而提高了血栓形成的易感性。刚性增加可能是由于细胞可变形性降低(主要取决于细胞骨架和细胞代谢能)或细胞质粘度降低(主要取决于血红蛋白浓度)引起的[39]。一些遗传性疾病的主要临床特征之一是红细胞变形性降低，镰状细胞病患者的红细胞膜比正常红细胞更为坚硬[40]，这主要是由于镰状血红蛋白在细胞内聚合，在缺氧条件下导致了红细胞的镰状化。

### 4.2. 启动凝血过程

有效的血液凝固需要足够的血栓前表面，以便正确组装凝血酶原复合物并产生凝血酶以启动凝血。这些表面由暴露磷脂酰丝氨酸(一种带负电的磷脂)的细胞提供，磷脂酰丝氨酸(PS)通常位于细胞质侧的膜上，并与血浆凝血因子分离[41]。带有 PS 的活化血小板被视为主要的血栓前表面，然而越来越多的证据表明，红细胞也可能通过暴露 PS 在血栓形成中发挥重要作用。在细胞凋亡或红细胞损伤或激活的情况下，例如高剪切应激、补体攻击、氧化应激或促凋亡刺激，红细胞膜失去 PS 不对称性[42]。此外，红细胞膜脂不对称性丧失通常伴随着微泡的起泡和随后的脱落，这些微泡在其表面暴露 PS。在体外，红细胞磷脂酰丝氨酸可以激活接触途径并支持凝血酶生成[43]。在体内，红细胞可能增强脂多糖处理的单核细胞的促凝活性并有助于在富含红细胞的静脉血栓中的凝血酶生成[44]。红细胞膜中磷脂酰丝氨酸暴露的显著例子是镰状细胞病和地中海贫血。在镰状细胞病中，突变血红蛋白反复聚集与解离，导致红细胞反复进行镰刀化以及非镰刀化的改变，并使得异常的磷脂酰丝氨酸暴露[45]。$\beta$-地中海贫血患者红细胞磷脂酰丝氨酸外露的增加与红细胞自杀性死亡(即溶血)有关[46]。

红细胞微泡是由红细胞衍生的细胞外微泡，细胞在体内产生微泡的能力是生理反应的重要调节机制，是细胞间通讯的一种手段，也是许多止血和血栓形成疾病的致病因素。在与红细胞相关的血栓前状态(如镰状细胞病和溶血性贫血)中，循环红细胞所产生的微泡数量增加。红细胞微泡的积累被认为是输注红细胞后深静脉血栓形成发生率增加的原因之一[47]。在一项与输血相关的血栓并发症研究中，发现红细胞微泡的促凝血活性和凝血时间与其含量显着相关，这表明微泡的含量越高，其促凝血活性越强，凝血时间越短[48]。红细胞微泡主要通过两种途径促进凝血酶的生成，一是通过直接激活 FXII 从而启动内源性凝血途径(FXIIa-FXI-FIX)，二是在前激肽释放酶依赖性途径中激活 FIX [49]。

### 4.3. 与内皮细胞相互作用

正常成熟的红细胞与内皮细胞之间通常不存在相互作用，然而，在某些病理条件下，红细胞会变得高度粘稠，这种异常红细胞与血管内皮细胞的黏附将导致微血管闭塞，进而促进血栓形成。基底细胞粘附分子、整合素 $\alpha 4\beta 1$、细胞间粘附分子 4 (ICAM-4)、血管细胞粘附分子 1 等粘附分子介导红细胞与内皮细胞的黏附作用[49] [50]。红细胞与内皮相互作用的常见病理状态包括镰状细胞病、疟疾和糖尿病。在贫血患者中，缺氧诱导的基因表达变化可能会改变内皮细胞表型，从而增加血栓形成的风险[51]。

### 4.4. 与血小板相互作用

在红细胞处于低氧分压、酸性环境和变形状态下，会释放出 ADP、ATP 和 TXA2，以促进血小板的粘附与聚集[52]。此外，溶血过程中释放的游离血红蛋白通过降低一氧化氮(NO)的生物利用度来促进血小板活化[53]。红细胞和血小板的聚集是由纤维蛋白原、细胞间粘附分子 4 (ICAM-4)和血小板整合素($\alpha$IIb$\beta$3)等粘附分子介导的[54] [55]。$\alpha$IIb$\beta$3 是 ICAM-4 的跨膜受体。红细胞和血小板的粘附可以通过糖蛋白 VI (GPVI)激动剂–惊厥剂和凝血酶增强，同时被生理浓度(3 mg/mL)的 EDTA、抗 CD36、抗 GPIb 抗体和可溶性纤维蛋白原阻断[56]。红细胞还会影响血小板与内皮细胞的粘附。Tokarev 等人的研究表明，红细胞体积越大，HCT 越高，血小板与内皮细胞的粘附越强，这一结论在人类、兔子和山羊中得到了验证[57]。

### 4.5. 与纤维蛋白原相互作用

在低剪切率条件下，红细胞形成 roleaux 结构需要纤维蛋白原的参与[58]。纤维蛋白原浓度增加可导致红细胞聚集增加，进而促进血栓形成。CD47 (整合素相关蛋白)、$\beta$3 整合素以及整合素样受体在纤维蛋白与红细胞的连接中发挥重要作用，而血管性血友病因子(VWF)也在其中扮演着关键角色[59]。XIIIa 是

一种源自血浆的转谷氨酰胺酶，通过与纤维蛋白 $\alpha$ 链进行共价交联，促进纤维蛋白聚合物因子连接，并有助于保留血栓内的红细胞，从而增加血栓体积[60]。抑制 XIIIa 有助于促进红细胞从血栓中排出。较高的血细胞比容导致血栓对组织纤溶酶原激活剂(tPA)的纤溶抵抗力增强，红细胞以剂量依赖性的方式降低血栓对溶栓的敏感性，从而增强凝块的稳定性[61]。

### 4.6. 与中性粒细胞相互作用

中性粒细胞在血栓形成过程中扮演着至关重要的角色，近年来，研究主要关注于中性粒细胞生成的 NETs 对血栓形成的影响[62]。NETs 主要由细胞外染色质组成。NETs 为血栓形成早期阶段的红细胞提供支架，同时改变体外毛细血管血流，导致红细胞发生机械损伤并产生大量碎片[63]。红细胞也可以影响 NETs。与 PM (经典的 NET 诱导剂)相比，血红素可以更快地诱导 NET 产生[64]。在储存的犬红细胞的上清液中检测到 66 个 NETs，并且随着储存时间的延长，上清液中游离 DNA 和 citH3 (NETs 标记物)的水平逐渐增加[64]，这表明了红细胞溶解后释放的游离血红蛋白对 NET 产生的影响。

## 5. 总结与展望

红细胞在静脉血栓形成过程中起到很大作用，可以通过改变血液流变学，促进凝血酶生成，影响内皮细胞、血小板、纤维蛋白原和中性粒细胞等来促进 DVT 生成。红细胞相关指标异常如血细胞比容、RDW、MCV 等变化等对骨创伤患者血栓性疾病发生及预后预测价值高，且操作相对简单，因此，在 DVT 的风险评估时应考虑红细胞相关指标异常。

随着对红细胞在血栓形成中作用的深入认识，开发针对红细胞的靶向抗血栓药物也成为可能。例如，阻断红细胞与纤维蛋白原或内皮细胞之间的相互作用可以分别通过阻止红细胞的聚集和粘附来减少深静脉血栓形成。因子 XIIIa 介导静脉血栓中红细胞保留的发现表明，抑制因子 XIIIa 可能有助于减小血栓体积并促进 VTE 的溶解。未来需要进行基础和转化研究以验证这些概念。

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