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· 专题研究 ·

ABO 血型与深静脉血栓发生风险关系的病例对照研究及 Meta 分析

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摘要

背景与目的: 深静脉血栓 (DVT) 是住院患者常见的并发症, 其病因复杂, 如何预防 DVT 的发生是临床工作的重点。本研究通过病例对照研究及 Meta 分析探讨 ABO 血型与 DVT 发生风险的关系, 以期为 DVT 的个体化预防及精准治疗提供依据。

方法: 选择 2012 年 10 月—2018 年 12 月苏北人民医院血管外科的 500 例住院 DVT 患者 (多次住院患者只统计首次住院), 并按诱因 (无明显诱因、妊娠、外伤、手术、癌症、长期卧床) 及性别 1:1 配对选择同期 500 例非 DVT 住院患者行病例-对照研究。检索多个国内外数据库收集相关病例-对照研究, 检索时间从建库至 2019 年 10 月 1 日, 根据纳入标准和排除标准筛选文献, 经质量评价及提取数据后, 采用 Review Manager 5.3 软件进行 Meta 分析。

结果: 病例-对照研究中, 整体分析结果显示, 非 O 型血较 O 型血个体 DVT 发生风险升高 ($RR=2.859$, $95\% CI=2.142\sim3.817$, $P<0.01$); 按诱因进行亚组分析, 结果显示, 在无明显诱因 ($RR=2.845$, $95\% CI=1.819\sim4.282$, $P<0.05$)、外伤 ($RR=3.11$, $95\% CI=1.477\sim6.552$, $P<0.05$)、手术 ($RR=2.613$, $95\% CI=1.271\sim5.373$, $P<0.05$) 及癌症 ($RR=2.962$, $95\% CI=1.436\sim6.106$, $P<0.05$) 患者中, 非 O 型血是 DVT 发生的可能危险因素, 而在妊娠 ($RR=1$, $95\% CI=0.034\sim29.807$, $P>0.05$) 及卧床 ($RR=5.714$, $95\% CI=0.528\sim30.325$, $P>0.05$) 患者未表现出明显关系。Meta 分析结果显示, O 型血个体发生 DVT 风险低于非 O 血型人群 ($RR=0.62$, $95\% CI=0.56\sim0.69$, $P<0.05$)。

结论: 对无明显诱因组、外伤组、手术组及癌症组患者, 将 ABO 血型纳入 DVT 危险因素的综合分析中, 对于血栓的个体化干预和精准治疗有一定临床价值。对于妊娠组及长期卧床组患者, ABO 血型的不同不一定能表现出足够临床价值, 仍需进一步验证。

关键词

静脉血栓形成; ABO 血型系统; 病例对照研究; Meta 分析; 危险因素
中图分类号: R654.3

Relationship between ABO blood group system and the risk of deep vein thrombosis: a case-control study and Meta-analysis

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Abstract

Background and Aims: Deep vein thrombosis (DVT) is a common complication of inpatients with complex etiology. How to prevent the occurrence of DVT is a major problem in clinical practice. This study was conducted to investigate the relationship between ABO blood groups and the risk of DVT through a case-control study and Meta-analysis, so as to provide evidence for the individual prevention and precise treatment of DVT.

Methods: Five hundred hospitalized patients with DVT from October 2012 to December 2018 in the Department of Vascular Surgery of North Jiangsu People's Hospital (only the first-time admission was counted in multiple-hospitalization patients), and 500 cause (no evident precipitating event, pregnancy, injury, surgery, cancer, and long-term bedridden) and sex 1:1 matched hospitalized patients without DVT during the same period were enrolled for a case-control study. The relevant case-control studies were collected by searching several national and international databases, and the retrieval time was limited from inception to October 1, 2019. After literature screening according to the inclusion and exclusion criteria, quality assessment and data extraction, Meta-analysis was performed by Review Manager 5.3 software.

Results: In case-control study, the results of overall analysis showed that the risk of DVT in individuals with O-type blood was significant higher than those with non-O-type blood ($RR=2.859$, $95\% CI=2.142-3.817$, $P<0.01$); the results of subgroup analysis stratified by causes showed that non-O-type blood was a possible risk factor for DVT in those with no obvious precipitating event ($RR=2.845$, $95\% CI=1.819-4.282$, $P<0.05$), having injury ($RR=3.11$, $95\% CI=1.477-6.552$, $P<0.05$), undergoing surgery ($RR=2.613$, $95\% CI=1.271-5.373$, $P<0.05$) and with cancer ($RR=2.962$, $95\% CI=1.436-6.106$, $P<0.05$), but had no significant significance in the those with pregnancy ($RR=1$, $95\% CI=0.034-29.807$, $P>0.05$) and the long-term bedridden ($RR=5.714$, $95\% CI=0.528-30.325$, $P>0.05$). Results of Meta-analysis showed that the risk of DVT in individuals with O-type blood was lower than those with non-O-type blood ($RR=0.62$, $95\% CI=0.56-0.69$, $P<0.05$).

Conclusion: For patients with no apparent cause, having injury, undergoing surgery or with cancer, incorporating the ABO blood groups into the comprehensive analysis of risk factors for DVT may have certain clinical value for individual intervention and precise treatment of thrombosis. For patients with pregnancy and long-term bedridden, ABO blood groups may not be of sufficient clinical value, which still need to be further verified.

Key words

Venous Thrombosis; ABO Blood-Group System; Case-Control Studies; Meta-Analysis; Risk Factors

CLC number: R654.3

深静脉血栓形成 (deep venous thrombosis, DVT) 是由于静脉血液异常凝集而引起的血液回流障碍, 是住院患者常见的并发症, 可表现为疼痛、肿胀、浅静脉曲张等^[1]。19世纪中期, Virchow提出静脉血栓形成的三大因素, 即静脉血流滞缓、静脉壁损伤和血液高凝状态^[2]。ABO血型系统的抗原(A、B和H)由置于红细胞膜外表面的复杂碳水化合物分子组成, 在我国ABO血型的表型分布频率随地区而变化, 从北向西南的方向, O基因频率逐渐升高, 频率分布大致为O型血35%, A型血28%, B型血29%, AB型血8%^[3]。人类血型作为一个遗传标记与多种疾病有关^[4]。Jick等^[5]早在1969年发现非O型血型人群似乎更容易产生DVT。随后Gándara等^[6-7]通过研究得到了相同的结果。但是, 在2002年的一项创伤后DVT患者

的回顾性研究中发现创伤患者DVT的发生与ABO血型之间没有关系^[8], 得出了与前述学者相反的结果。目前对于ABO血型与DVT的关系仍有争议。本文在统计苏北人民医院的DVT病例基础上, 通过检索PubMed、CNKI、SionMed、万方、维普等数据库筛选相关文献, 进行ABO血型系统与DVT发生风险的病例-对照研究及相关Meta分析, 以期更好地明确ABO血型与DVT发生可能存在的关联, 为DVT的个体化预防及精准治疗提供依据。

1 资料与方法

1.1 病例-对照研究

对苏北人民医院2012年10月—2018年12月的500例住院DVT患者(多次住院患者只统计首次住

院)进行统计,按诱因分为无明显诱因组、妊娠组、外伤组、手术组、癌症组、长期卧床组。其中无明显诱因组267例(排除其他诱因,无阳性诊断),妊娠组3例(产褥期),外伤组73例(四肢及多发骨折患者),手术患者74例(排除骨折手术患者),癌症患者72例,长期卧床患者11例(因脑梗、昏迷及脊柱损伤卧床,平均卧床时间为 (64.45 ± 67.32) d,明确其年龄及血型分布。对照组按诱因1:1配对选取该院500例非DVT住院患者。对病例组和对照组进行统计学分析,计算不同诱因下患者的年龄(独立样本 t 检验)及血型(RR值及95% CI)与DVT发生的危险程度。

1.2 文献系统评价

1.2.1 检索策略与文献提取 检索PubMed、CNKI、SionMed、万方、维普数据库,文献语种不限,起始时间不限,截止时间为2019年10月1日,英文检索词包括:ABO Blood Group System; ABO Blood Group Systems; ABO Blood Group、H Blood Group System; H Blood Group; Blood Groups; H Blood Groups; ABH Blood Group; ABH Blood Groups; Blood Group H Type 1 Antigen; ABO Factors; ABO Factor; Venous Thrombosis; Phlebothrombosis; Phlebothromboses; Venous Thrombose; Deep Vein Thrombosis; Deep Vein Thromboses等。中文检索词包括:ABO血型系统;静脉血栓形成等。手工检索正在进行的病例-对照研究、专题报告、未发表的资料、会议文献等。由2名研究人员独自阅读文题及摘要筛选相关文章,通过阅读全文对相关文献的研究设计、纳入排除标准、对照情况及研究结果判断方式进行评估,根据纳入排除标准选择是否将文件纳入Meta分析。如存在争议,交由第3名研究人员重新评估,并决定是否纳入分析。

1.2.2 文献纳入排除标准 纳入标准:(1)研究类型为病例-对照研究;(2)文中病例组及对照组相关数据,均应由作者亲自调查所得;(3)对照组与病例组具有可比性(如选取同一医院同期的非DVT患者作为对照);(4)诊断标准明确,病例组DVT患者符合诊断标准;(5)基于同一样本的文献,只选取其中最详细数据报告的文献。排除标准:(1)文摘、综述等二、三次文献;(2)病例组、对照组样本的选取由他人文献加工而来;(3)对照组与病例组无可比性(如选择的人口样本不处于同一时期、存在区域差异,或选取特殊人群造成混杂影

响);(4)无明确诊断标准,病例组未明确诊断证实;(5)无法获取详细资料的文献。

1.2.3 文献质量评价 由2名研究人员独立采用纽卡斯尔-渥太华量表(the Newcastle-Ottawa scale, NOS)对纳入分析的文献进行评价,如有分歧采用第三方意见^[9]。按NOS量表评价内容分8个给分条目、9个给分点,每点评1分:(1)研究人群的选择。病例选择是否恰当?是否有代表性?对照组的选择是否与病例组为同一人群对照?如何确定对照组?每点1分,共4分。(2)组间可比性。研究设计和统计分析时是否考虑病例组和对照组的可比性,对混杂因素是否控制?年龄、种族、区域、性别、样本结构等均视为重要混杂因素,凡控制一项者评1分,共2分。(3)对暴露因素的确定。如何对暴露因素进行确定?是否采取相同的方法确定病例组和对照组的暴露因素?两组的无应答率?每点1分,共3分。总评分>6分的文献认为是高质量。

1.3 统计学处理

采用ReviewManager 5.3软件进行Meta分析,采用比值比(OR)为效应量,各效应量均以95% CI表示。各纳入研究结果间的异质性采用 I^2 检验,当各研究间异质性可接受($I^2 < 50%$)时,采用固定效应模型进行Meta分析;若各研究间存在统计学异质性($I^2 \geq 50%$),分析其异质性来源,如无临床异质性,采用随机效应模型进行分析。

2 结果

2.1 病例-对照研究结果分析

本研究共纳入DVT组患者500例,平均年龄(61.59 ± 13.04)岁。并按病因、性别1:1配对选取500例无血栓患者作为对照,平均年龄(57.16 ± 16.58)岁。DVT组患者的平均年龄较对照组患者高,采取独立样本 t 检验($t=4.7$, $P < 0.01$),具有统计学意义。500例DVT患者中,O型血196例(39.2%),非O型血304例(60.8%)。500例非DVT对照组患者中,O型血92例(18.4%),非O型血408例(81.6%)。统计后发现,非O型血较O型血个体血栓发生风险升高(RR=2.859, 95% CI=2.142~3.817),经 χ^2 检验后,具有统计学意义($\chi^2=52.747$, $P < 0.01$)(表1)。

考虑到有多种因素可能会影响到DVT的形成,将500例DVT患者按病因分为无明显诱因者

267例(53.4%)、妊娠者3例(0.60%)、外伤者73例(14.60%)、手术者74例(14.80%)、肿瘤者72例(14.40%)、长期卧床者11例(2.20%)。分别计算各组患者特征及血分布,从而排除不同诱因带来的误差(表2)。其中在无明显诱因组、外伤组、手术组中DVT患者较非DVT患

者年龄较高,非O型血较O型血发生DVT的可能性增加(均 $P<0.05$)。在癌症患者组只有非O型血与DVT形成有统计学意义($P=0.003$)。而在妊娠组及卧床组患者中,年龄及血型在DVT行程中未表现出统计学差异(均 $P>0.05$)。

表 1 DVT 组与对照组特征与血型分布比较

Table 1 Comparison of the features and blood group distribution between DVT group and control group

参数	对照组	DVT 组	RR	95% CI	t/χ^2	P
年龄(岁, $\bar{x} \pm s$)	57.16 ± 16.58	61.59 ± 13.04	—	—	4.7	<0.01
性别 [n (%)]						
男	250 (50.0)	250 (50.0)	—	—	—	—
女	250 (50.0)	250 (50.0)				
血型 [n (%)]						
O 型	196 (39.2)	92 (18.4)	2.859	2.142~3.817	52.747	<0.01
非 O 型	304 (60.8)	408 (81.6)				

表 2 DVT 组与对照组特征与血型分布的亚组分析

Table 2 Subgroup analysis of the features and blood group distribution between DVT group and control group

参数	对照组	DVT 组	RR	95% CI	t/χ^2	P
无明显诱因						
年龄(岁, $\bar{x} \pm s$)	58.18 ± 16.86	62.80 ± 13.10	—	—	3.524	<0.01
血型 [n (%)]						
O 型	96 (36.0)	44 (16.5)	2.845	1.819~4.282	26.177	<0.01
非 O 型	171 (64.0)	223 (83.5)				
妊娠						
年龄(岁, $\bar{x} \pm s$)	25.67 ± 3.06	26.33 ± 1.16	—	—	0.354	0.742
血型 [n (%)]						
O 型	1 (33.3)	1 (33.3)	1	0.034~29.807	0	1
非 O 型	2 (66.7)	2 (66.7)				
外伤						
年龄(岁, $\bar{x} \pm s$)	55.14 ± 19.12	59.89 ± 11.51	—	—	1.820	0.071
血型 [n (%)]						
O 型	31 (42.5)	14 (19.2)	3.111	1.477~6.552	9.284	0.002
非 O 型	42 (57.5)	59 (80.8)				
手术						
年龄(岁, $\bar{x} \pm s$)	50.23 ± 15.31	59.11 ± 13.27	—	—	3.770	<0.01
血型 [n (%)]						
O 型	31 (41.9)	16 (21.6)	2.613	1.271~5.373	7.015	0.008
非 O 型	43 (58.1)	58 (78.4)				
癌症						
年龄(岁, $\bar{x} \pm s$)	63.50 ± 9.15	62.28 ± 12.12	—	—	-0.683	0.495
血型 [n (%)]						
O 型	33 (45.8)	16 (22.2)	2.962	1.436~6.106	8.940	0.003
非 O 型	39 (54.2)	56 (77.8)				
卧床						
年龄(岁, $\bar{x} \pm s$)	59.55 ± 11.09	65.45 ± 11.79	—	—	1.211	0.240
血型 [n (%)]						
O 型	4 (36.4)	1 (9.1)	5.714	0.528~30.325	2.329	0.127
非 O 型	7 (63.6)	10 (90.9)				

2.2 Meta 分析结果

2.2.1 检索结果 根据检索策略, 排除重复文献, 共检索出文献 137 篇。经纳入、排除标准检验后, 最终纳入文献 30 篇 (图 1), 其基本资料见表 3。

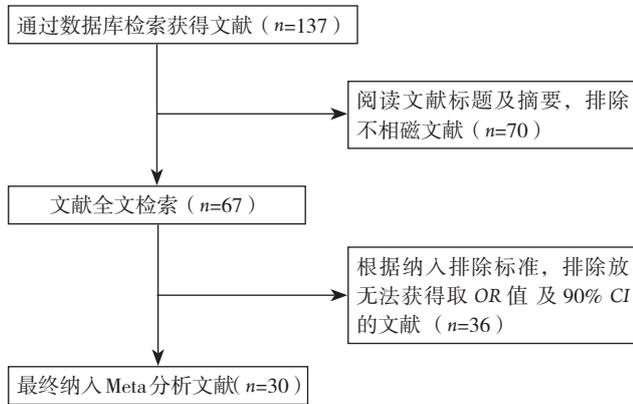


图 1 文献筛选流程图

Figure 1 Literature screening process

表 3 纳入文献基本特征 (n)

Table 3 General characteristics of the included studies (n)

纳入研究	年份	DVT 组		对照组	
		O 型血例数	总人数	O 型血例数	总人数
Ahmed, 等 ^[10]	2015	46	148	80	148
Bhanvadiah, 等 ^[11]	2019	27	90	568	1251
Carter, 等 ^[8]	2002	153	343	162	343
Cohen, 等 ^[12]	2012	32	161	541	1613
Jick, 等 ^[13]	1978	16	86	157	344
Li, 等 ^[14]	2015	73	434	178	236
Mizrahi, 等 ^[15]	2015	14	56	207	467
Nascimento, 等 ^[16]	2015	12	44	14	26
Ohira, 等 ^[17]	2007	175	492	479	1008
Paiva, 等 ^[18]	2009	31	148	130	233
Ribeiro, 等 ^[19]	2016	1 158	4 062	2 146	4 659
Robinson, 等 ^[20]	1980	37	125	157	333
Shusterman, 等 ^[21]	2018	31	75	81	151
Spiezia, 等 ^[22]	2013	58	249	108	244
Suchon, 等 ^[23]	2016	227	968	323	874
Sun, 等 ^[24]	2017	340	1 412	60 118	199 248
Sun, 等 ^[25]	2015	60	214	286	636
Teixeira, 等 ^[26]	2009	52	175	98	175
Tufano, 等 ^[27]	2013	19	77	1 900	4 272
van Adrichem, 等 ^[28]	2015	1 024	3 682	2 220	4 657
van Langevelde, 等 ^[29]	2011	1 130	3 925	2 149	4 667
白璐 ^[30]	2016	25	154	41	154
郭海 ^[31]	2017	5	34	38	110
齐典文, 等 ^[32]	2014	3	24	28	66
王美堂, 等 ^[33]	2004	8	57	45	128
王燕玲, 等 ^[34]	2017	71	181	25	93
席少枝 ^[35]	2012	8	48	14	48
于连有 ^[36]	2016	21	30	12	30
赵海歌 ^[37]	2017	14	73	56	146
周稳, 等 ^[38]	2015	21	30	52	82
合计		5 111	18 309	72 767	227 154

2.2.2 纳入文献的质量评价 采用 NOS 量表对纳入的文献进行质量评价, 各纳入文献总评分均 >6 分, 为高质量文献 (表 4)。

表 4 纳入文献 NOS 量表

Table 4 The NOS scale of the included studies

纳入研究	年份	研究人群的选择	组间可比性	暴露因素的测量	合计
Ahmed, 等 ^[10]	2015	4	1	3	8
Bhanvadiah, 等 ^[11]	2019	3	1	3	7
Carter, 等 ^[8]	2002	2	2	3	7
Cohen, 等 ^[12]	2012	4	1	3	8
Jick, 等 ^[13]	1978	4	2	3	9
Li, 等 ^[14]	2015	4	2	3	9
Mizrahi, 等 ^[15]	2015	4	2	3	9
Nascimento, 等 ^[16]	2015	3	1	3	7
Ohira, 等 ^[17]	2007	4	0	3	7
Paiva, 等 ^[18]	2009	4	1	3	8
Ribeiro, 等 ^[19]	2016	4	2	3	9
Robinson, 等 ^[20]	1980	3	1	3	7
Shusterman, 等 ^[21]	2018	3	1	3	7
Spiezia, 等 ^[22]	2013	4	1	3	8
Suchon, 等 ^[23]	2016	4	2	3	9
Sun, 等 ^[24]	2017	4	2	3	9
Sun, 等 ^[25]	2015	4	2	3	9
Teixeira, 等 ^[26]	2009	4	2	3	9
Tufano, 等 ^[27]	2013	3	1	3	7
van Adrichem, 等 ^[28]	2015	4	2	3	9
van Langevelde, 等 ^[29]	2011	4	0	3	7
白璐 ^[30]	2016	4	2	3	9
郭海 ^[31]	2017	4	2	3	9
齐典文, 等 ^[32]	2014	3	1	3	7
王美堂, 等 ^[33]	2004	4	1	3	8
王燕玲, 等 ^[34]	2017	4	1	3	8
席少枝 ^[35]	2012	4	2	3	9
于连有 ^[36]	2016	4	1	3	8
赵海歌 ^[37]	2017	4	2	3	9
周稳, 等 ^[38]	2015	4	0	3	7

2.2.3 Meta 分析结果 在纳入的 30 篇文献中, DVT 组 O 型血 4 891 例 (27.79%), 对照组 O 型血 72 413 例 (31.98%), 经异质性分析, 整体存在异质性 ($I^2=87\%$, $P<0.01$), 采取随机效应模型, Meta 分析结果显示 O 型血较非 O 血型在 DVT 发生风险上差异存在统计学意义 ($RR=0.62$, $95\% CI=0.56\sim 0.69$, $P<0.05$) (图 2)。

2.2.4 发表偏倚分析 绘制倒置漏斗图发现, 纳入的 30 篇文献完整地出现在图上, 各亚组以合并效应量 RR 值为中心散开分布, 基本对称, 小样本的效应点基本分布在底部, 大样本逐渐趋于在上部一个较窄的范围内, 呈倒置漏斗形 (图 3)。

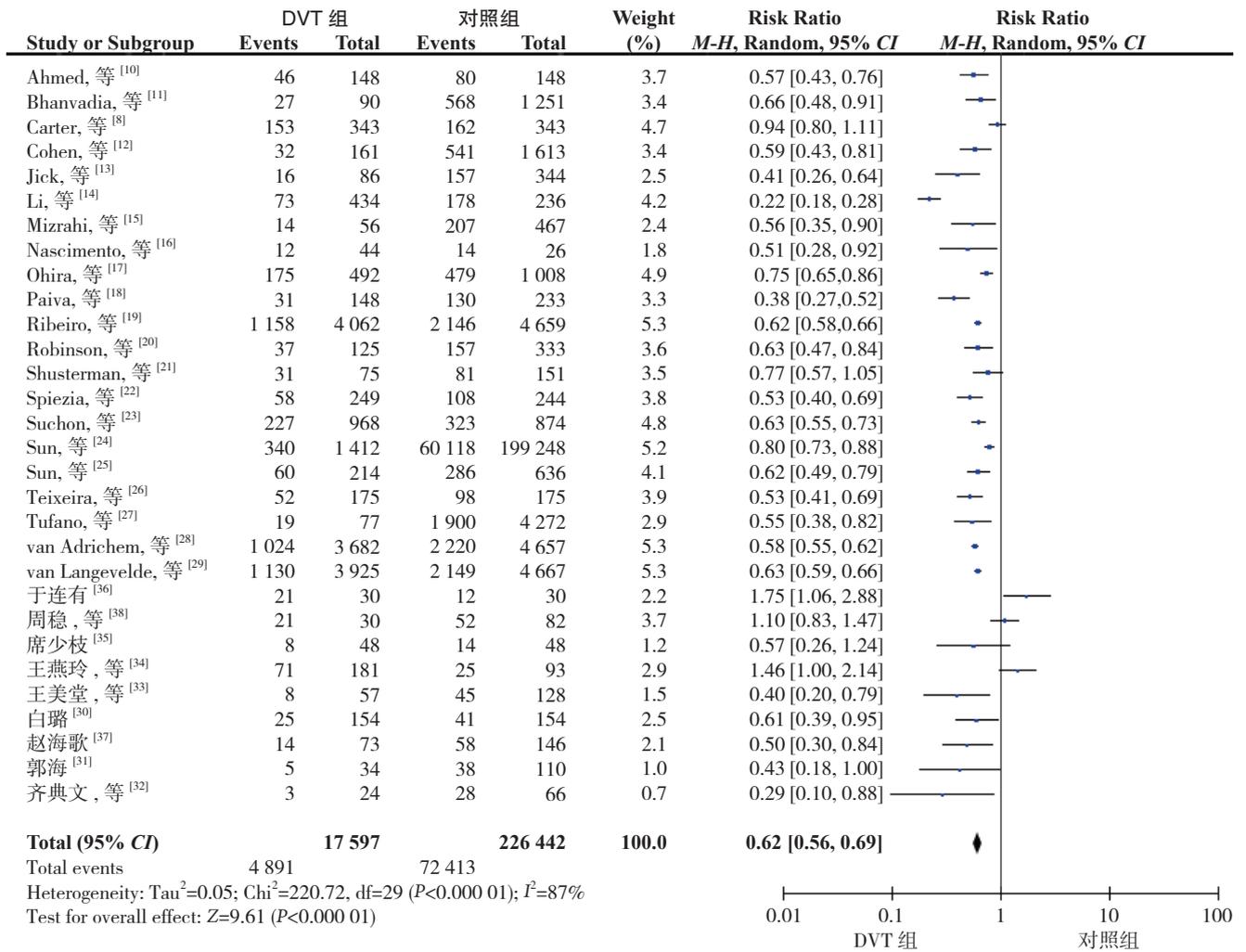


图 2 森林图

Figure 2 The forest plot

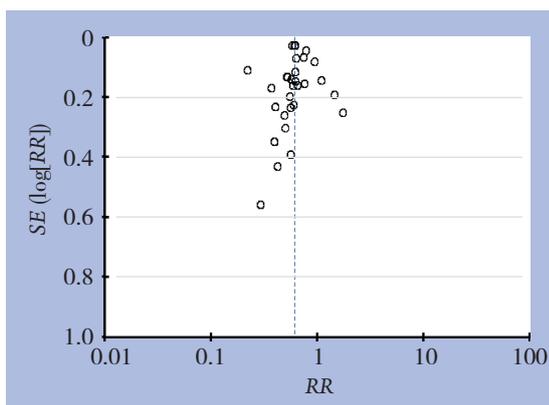


图 3 漏斗图

Figure 3 The funnel plot

3 讨论

ABO血型系统的抗原(A、B和H)由置于红细胞膜外表面的复杂碳水化合物分子组成^[39]。其

抗原基因位于9号染色体长臂(9q34.2),但并不是染色体直接编码抗原。ABO抗原是从共同的前体物质加工而来的。前体物质会在岩藻糖基转移酶的催化下形成H抗原,即O型血个体。然后在各自催化酶的作用下加上不同的基因形成A、B型血^[40],所以在结构上非O型血个体的血型抗原较O型血个体复杂,可能产生不同的生理功能。

DVT是住院患者中发病率比较高的一类疾病^[41]。目前,临床上治疗DVT的患者时,通常是询问有没有长期卧床、手术、外伤、妊娠、癌症等病史,而在预防DVT形成方面,也同样是重点针对这些方面。但是DVT形成在病因学上是多样性的,除了继发性因素外,还有许多原发性因素包括抗凝血酶缺乏症、因子VII缺乏症、纤溶酶原缺乏症、因子V Leiden突变、凝血酶原基因G20210A突变、蛋白C缺乏症、蛋白S缺乏症、高半胱氨酸血症等^[42]。因此该疾病个体差异较大,无明显诱

因的患者仍占大多数。

归因于DVT病因学的复杂性,目前关于ABO血型系统对DVT的影响仍有争论,且ABO血型与DVT形成之间关系的机制尚不清楚。有研究^[43-44]表明,ABO血型系统与血管性血友病(Von Willebrand, VWF)的水平密切相关。Schleef等^[45]研究显示,O型血人群的vWF水平为654~1 028 U/L,而非O型血人群其vWF水平为900~1 390 U/L,平均水平为1 339 U/L。

vWF是由内皮细胞、巨核细胞分泌的一种分子量不等的多聚体,可以通过介导血小板与内皮下胶原的黏附反应、介导血小板与血小板之间的聚集、作为凝血因子Ⅷ的保护性载体来促进血栓形成。vWF会在金属蛋白酶ADAMTS13的催化下裂解,最终成为没有功能的蛋白水解片段。

ABO抗原系统影响血栓形成的机制可能在于其抗原通过寡糖链存在于vWF之上,不同血型的寡糖链不同,会影响到vWF结构的位阻和电荷效应,从而会影响金属蛋白酶ADAMTS13的作用,进而影响裂解速率^[46-47]。另外vWF起初是以大型复合物的形式存在的,当内皮受损后,紧密折叠的vWF会在血流的作用下变疏松,暴露作用基团,产生生物活性。寡糖链的不同,可能会影响vWF结构的变化速率。

本研究通过病例对照研究发现对于无明显诱因、外伤、手术、癌症的患者ABO抗原系统与DVT发生之间存在相关性。而对于妊娠及长期卧床患者未能证明相关性,考虑到妊娠及卧床患者病例数目较少,该结论有待进一步扩大样本进行验证。通过纳入30篇临床对照研究进行的Meta分析也进一步证实了O型血对DVT患者的保护作用,差异有统计学意义。

综上所述,于无明显诱因、外伤、手术、癌症的患者将ABO血型纳入DVT危险因素的综合分析中,对于血栓的个体化预防及精准治疗有一定临床价值。对于妊娠组及长期卧床组患者,ABO血型的不一定能表现出足够临床价值。考虑到妊娠及卧床患者病例数目较少,结论仍需进一步验证。

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