肺移植后的非感染性并发症

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我们的所有专题都会依据新发表的证据和同行评议过程而更新。

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There is a newer version of this topic available in English. 该主题有一个新的英文版本。

引言

对特定的终末期肺病患者来说，肺移植是一项重要的治疗选择，可能提高患者的生存质量和远期生存率。但肺移植受者可发生妨碍肺移植的多种感染性和非感染性并发症，包括吻合口问题、移植物排异反应、原发性移植肺功能丧失、膈神经损伤、胸腔并发症、静脉血栓栓塞症(venous thromboembolism, VTE)、移植后恶性肿瘤及原发疾病复发。

本文将总结肺移植的一般非感染性并发症。其他移植相关并发症见其他专题，如气道吻合口并发症、胃食管反流、肌力减弱、感染和移植物排斥反应。(参见 “肺移植后气道并发症”和 “肺移植后的生理变化”和 “肺移植后真菌感染”和 “肺移植术后的细菌感染”和 “肺移植受者巨细胞病毒感染的临床表现、诊断和治疗”和 “Viral infections following lung transplantation”和 “急性肺移植排斥反应的评估和治疗”和 “慢性肺移植物功能丧失：闭塞性细支气管炎”)

移植物排斥反应

急性和慢性肺移植排斥反应见其他专题。(参见 “急性肺移植排斥反应的评估和治疗”和 “抗体介导肺移植排斥反应的评估和治疗”和 “慢性肺移植物功能丧失：闭塞性细支气管炎”)

吻合口并发症

肺移植过程需要完成3种吻合：气道吻合、肺动脉吻合及肺静脉-左心房吻合。

气道吻合口并发症 — 气道吻合口并发症见其他专题。(参见 "肺移植后气道并发症")

血管吻合口并发症 — 动脉吻合口和静脉吻合口的并发症虽然较气道吻合口并发症少见，但可能产生毁灭性影响。血管并发症包括狭窄、动脉扭曲及血栓形成。

肺动脉狭窄 — 肺动脉狭窄在肺移植后早期和晚期都有报道。其原因包括：供者和受者的肺动脉段过长、供者肺动脉段过短引起的扭曲、操作技术引起的缩窄、吻合口扭转及血栓形成[1]。呼吸急促等症状以及肺高压和右心衰竭(如，体循环低血压或外周性水肿)等体征可提示这一诊断。患者可能存在右心室压增高或右心室功能不全的超声心动图证据[2]。定量的肺通气/灌注扫描可显示，双肺移植后两侧肺间的血流分布不均，或单肺移植后血液不成比例地流向自体肺。CT血管造影和动态MR血管造影也可能提示诊断；然而，肺血管造影对于确诊肺动脉吻合口狭窄通常必不可少(包括证明压力梯度>10mmHg)，同时可实施气囊扩张及支架放置等治疗措施[2-4]。对于其他干预措施治疗无效的肺动脉狭窄，手术重建是最终选择[5]。

肺动脉扭曲 — 已有在病例报道描述了肺动脉吻合口扭曲，其临床表现与肺动脉狭窄相似[6,7]。在一例病例中，经食管超声心动图结果显示，扭曲与肺静脉血流量下降有关[6]。经皮置入金属支架对两例肺动脉扭曲病例都有效。

肺静脉血栓形成 — 肺静脉血栓形成通常发生于术后早期，但在术后2周发病的情况也有报道[8]。肺静脉/左心房吻合口缝合线处的血栓形成有引发体循环栓塞和脑血管意外事件的风险[9]。血栓也可能妨碍肺静脉血液流出，造成药物难以治疗的严重肺水肿[10,11]。一项前瞻性队列研究通过在移植术后48小时内行经食管超声心动图检查，评估了87例连续肺移植受者中肺静脉血栓形成的发生率[10]。13例患者(15%)有提示肺静脉/左心房血凝块的证据。这组患者的死亡风险显著增高(90日死亡率为38%)。

临床特征包括低氧血症、肺顺应性降低和X线摄影显示移植肺出现弥漫性阴影，不过常规的经食道超声心动图检查也可发现一些临床上未怀疑的肺静脉血栓[12,13]。肺动脉压和中心静脉压可能升高。鉴别诊断包括肺静脉狭窄、原发性移植肺功能丧失、心肌功能障碍、感染和急性排斥反应[13]。通常经食管超声心动图检查诊断肺静脉血栓形成。

对于肺移植术后的肺静脉血栓形成，目前没有标准的治疗方法。如果出血风险并不高，有症状的血栓形成患者可受益于全身性抗凝，并可能受益于溶栓治疗[13]。难治的低氧血症和/或血流动力学不稳定可能需要紧急行手术取栓，但结局通常较差[14,15]。另一方面，有2例在静脉吻合口出现微小血栓，血流速度未增加的患者仅接受了监测而并未采取特异性治疗，结果其血栓自行消失。

膈神经和膈肌功能障碍

据报道，肺移植后膈肌麻痹的发病率为3%-9%[16-18]。膈神经损伤在心肺移植后更为常见；一项回顾性报道显示，超过40%的心肺移植受者出现了这一并发症。(参见 "成人心肺移植"，关于'膈神经功能障碍'一节)

目前认为，膈神经功能障碍的发病机制包括术中胸骨回缩、心包操作和纵隔剥离引起的机械性损伤，以及采用心脏局部低温麻痹时的低温损伤。

如果患者术后出现呼吸困难、低氧血症、通气不足、肺不张、直立位胸片所示半侧膈肌抬高或难以撤掉呼吸机，应怀疑有膈肌麻痹[19]。单侧膈肌麻痹一般是通过横膈的透视检查诊断，双侧膈肌麻痹则可根据具体临床情况、横膈双侧抬高、仰卧位和坐位肺量计检查、膈肌肌电图(electromyography, EMG)而高度怀疑。膈肌麻痹的诊断和治疗见其他专题。(参见 “成人单侧膈肌麻痹与膈膨出的病因和诊断”和 “双侧膈肌麻痹的病因与诊断”和 “膈肌麻痹的治疗”)

肺移植术后膈肌功能障碍可导致住院时间延长和机械通气时间延长[16,17,19-21]。

胸腔并发症

胸腔并发症在肺移植术后常见，包括气胸、支气管胸膜瘘、胸腔积液、血胸、脓胸及乳糜胸。这些并发症见其他专题。(参见 “肺移植术的胸膜并发症”)

原发性移植肺功能丧失

原发性移植肺功能丧失也称为原发性移植肺衰竭、严重缺血-再灌注肺损伤或肺再植反应，是一种发生在肺移植术后72小时内的严重、急性肺损伤综合征。其特点是X线摄影所示移植肺弥漫性阴影，以及肺泡-动脉氧分压差增大。原发性移植肺功能丧失见其他专题。(参见 “Primary lung graft dysfunction”)

静脉血栓栓塞症

与其他进行大型手术的患者相同，肺移植受者发生VTE的风险增加。报道显示，肺栓塞的发生率为5%-15%，而VTE的发生率为20%-45%(包括上下肢血栓)[22-25]。VTE最常发生于移植后早期，大多数事件在移植后数周至数月出现[26,27]。肺移植受者的VTE危险因素包括：高龄、既往VTE、男性、长期机械通气和住ICU、糖尿病、肺炎、体外膜肺氧合(extracorporeal membrane oxygenation, ECMO)和体外循环[23-25,27,28]。一项比较肺移植后他克莫司/西罗莫司/泼尼松与他克莫司/硫唑嘌呤/泼尼松的随机试验显示，西罗莫司组VTE风险高于硫唑嘌呤组(17% vs 3%)[29]。上肢VTE常与中心静脉置管有关[24]。

术后康复阶段肺动脉储备能力往往有限；因此，移植肺中出现栓子可造成严重后果[30]。血栓栓塞的表现是非特异性的，因此如果移植受者出现呼吸困难、低氧血症或运动诱导去氧饱和，需要高度警惕。一般通过CT肺血管造影(computed tomography pulmonary angiography, CTPA)或通气-灌注扫描(禁忌使用造影剂时)诊断VTE。其治疗与一般人群中的VTE治疗相同，但血胸的发生风险可能更大。VTE的诊断和治疗见其他专题。(参见 “下肢深静脉血栓治疗概述”和 “疑似急性肺栓塞非妊娠成人的临床表现、评估与诊断”和 “成人急性肺栓塞的治疗、预后和随访”和 “非妊娠成人疑似下肢深静脉血栓形成的临床表现和诊断”)

肺移植受者应采用标准的VTE预防性治疗，但尚未在该人群中前瞻性评估这些方式(及更长期的预防)[26]。(参见 “成人非骨科手术患者中静脉血栓栓塞症的预防”)

对于肺移植受者中留置中心静脉导管相关深静脉血栓形成，应采用常规方法评估和治疗。尤其是对于术前和/或术后应用大套管实施ECMO以辅助移植的患者，应高度警惕这一并发症。(参见 “导管相关性上肢静脉血栓形成”和 “成人体外膜肺氧合技术”，关于‘血栓栓塞’一节)

恶性肿瘤

实体器官移植受者的恶性肿瘤发生风险是一般人群的2倍[31,32]。据报道，肺移植后生存5年的受者中，超过17%的病例恶性肿瘤是死亡的近因[33]。(参见 “实体器官移植后发生恶性肿瘤”)

肺癌 — 由于肺移植的主要指征是吸烟相关疾病(如肺气肿、特发性肺纤维化)和相关更大的肺癌风险，单肺移植受者似乎比双肺移植受者更可能发生肺癌(见于自体肺)[34-41]。

在因多灶性或弥漫性细支气管肺泡癌而进行肺移植的患者中，肺癌也可能是疾病复发，细支气管肺泡癌现称为原位腺癌，病理学上分为贴壁生长为主型腺癌或黏液型腺癌[42-46]。一项回顾性多中心研究纳入1981-2001年间2168例连续肺移植受者(975例单肺移植，1211例双肺或心肺移植)，报道单肺移植受者中的支气管肺癌发生率是2%[47]。所有病例均发生在自体肺，双肺或心肺移植受者中没有病例报道。在另一项研究中，520例肺移植受者中发现了12例肺癌，其中11例位于自体肺[36]。这些研究中的肺癌发生率似乎并未超过高危患者，包括吸烟者和慢性阻塞性肺病(chronic obstructive pulmonary disease, COPD)/特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)患者，但高于一般人群[47-50]。一项回顾性研究纳入了来自美国移植受者科学登记系统的数据，发现肺移植受者的肺癌发生风险是一般人群的5.5倍[31]。需要注意，因为现今是根据肺脏分配评分(lung allocation score, LAS)来分配肺脏，通常会优先考虑等候名单上死亡风险最大的患者，肺癌患病率可能在增加；在一项大型单中心研究中，在引入LAS前切除病肺中偶然检出肺癌率为0.8%，在2005年5月引入LAS后为2.5%[51]。

移植肺极少发生支气管肺癌，这可能是由于供者都经过了仔细筛选，而高龄、大量吸烟和有肺实质病变证据的人群，其器官不适合用于移植[52]。然而，由于对移植肺的需求越来越大，人们开始考虑放宽肺脏供者的标准，纳入有大量烟草暴露史的个体。未来供者源性肺癌的发病率是否会增加还有待观察[53,54]。(参见 “肺移植的死亡供体评估”，关于‘扩大供体标准’一节)

虽然肺移植后的肺癌发生风险主要与常见危险因素相关，但在免疫抑制的影响下，肺癌的侵袭性似乎更强[35]。实际上，肿瘤进展可能非常迅速，以致与感染性疾病难以区分[40]。促进肿瘤生长是由于免疫抑制宿主中抗肿瘤免疫监测的丧失，还是所用免疫抑制药的特性，目前尚不清楚[55,56]。

肺结节的评估见其他专题。(参见 “偶发性肺结节的诊断性评估”)

移植术后淋巴细胞增生性疾病 — 移植术后发生的多种淋巴细胞增生性疾病(包括淋巴瘤)统称为移植术后淋巴细胞增生性疾病(posttransplantation lymphoproliferative disorder, PTLD)。其中包括一组具有形态和克隆异质性的B细胞异常增殖反应，这些反应与EB病毒感染相关，既有传染性单核细胞增

多样疾病和多克隆增生等良性病变，也有侵袭性恶性单克隆淋巴瘤。PTLD常起自受者的淋巴细胞，在肺移植受者中的发生率为3%-8%，高于其他实体器官(心、肝、肾)移植受者[57-61]。值得注意的是，与EB病毒感染无关的PTLD的发生率正在增加，最近一项研究报道，仅有约半数的PTLD病例与EB病毒有关[62]。在肺移植后可能发生的所有肿瘤中，PTLD的发生率仅次于非黑素瘤皮肤癌。PTLD的临床表现、诊断及治疗见其他专题。(参见 “移植后淋巴增殖性疾病的流行病学、临床表现和诊断”和 “移植后淋巴增殖性疾病的治疗和预防”)

以下内容将讨论肺移植受者所特有的问题。PTLD的临床表现因移植术后的时间而异，胸腔内或移植肺受累更常见于术后第1年内发病的病例，而胸腔外表现更常见于之后发病的病例[44,63]。在肺移植受者中，PTLD胸腔内表现可能是单个或多个肺结节或肿块、纵隔淋巴结肿大和胸腔积液[64-66]。弥漫性淋巴结肿大，以及胃肠道、泌尿生殖系统、乳房、皮肤和中枢神经系统受累也有报道[65,67-73]。

术前EB病毒血清阴性而术后出现原发性EB病毒感染的肺移植受者中PTLD的发生风险显著增加[74-77]。因此，儿童和年轻成人中的PTLD风险更高，并且在伴有囊性纤维化(cystic fibrosis, CF)的肺移植受者中，术前EB病毒血清阴性可能是PTLD发生率较高的原因，不过CF特异性危险因素可能也起一定作用[78,79]。较大的免疫抑制强度也与发生PTLD相关[74,76,80]。采用新型免疫抑制剂的PTLD发生风险尚不明确，必须密切监测。特别是如果考虑对肺移植受者超适应证使用贝拉西普(一种选择性T细胞共刺激阻滞剂)，须注意，有报道称，接受贝拉西普的肾移植受者中PTLD发病率增加[81-83]。(参见 “成人肾移植的维持性免疫抑制治疗”，关于‘使用钙调磷酸酶抑制剂后出现毒性的患者’一节)

肺移植后PTLD的初始治疗通常包括降低维持性免疫抑制的强度，使受者的EB病毒特异性细胞毒性T细胞能够恢复。然而，免疫抑制强度的降低可增加移植物排斥反应的发生风险[60,84]。除了降低免疫抑制强度，患者对CD20单克隆抗体利妥昔单抗也有良好的耐受，有效率达到50%-80%[65,69,85]。如果利妥昔单抗治疗无效或初始有效但随后病情复发，其他治疗选择有细胞毒化疗、放疗或放化疗结合[65,86-88]。化疗通常仅用于难治性且EB病毒及CD20均为阴性的肿瘤。对于巨大的肿块，特别是在胃肠道，可考虑手术干预以降低肠穿孔的风险。过继免疫治疗可输入来自受者(自体)或HLA匹配EB病毒阳性供者的细胞毒性T细胞，目前正在研究阶段[89]。具体治疗的作用见其他专题。(参见 “移植后淋巴增殖性疾病的治疗和预防”)

尚不清楚预防性抗病毒治疗对肺移植受者的作用，但许多儿科中心会监测EB病毒血清阴性受者是否有病毒激活的证据。早期检出原发性EB病毒感染时的预防性抗病毒治疗见其他专题。(参见 “移植后淋巴增殖性疾病的治疗和预防”，关于‘预防’一节)

原发疾病复发

已报道一些疾病可在移植肺中复发，包括：

- 肺结节病[90-95]
- 淋巴管平滑肌瘤病[96-98]

- 弥漫性泛细支气管炎[99]
- 肺泡蛋白沉积症[100,101]
- 脱屑型间质性肺炎[102]
- 肺朗格汉斯细胞组织细胞增生症[103-106]
- 细支气管肺泡癌[42,43,107]
- 特发性肺含铁血黄素沉着症[108,109]
- 巨细胞间质性肺炎[110]
- α-1抗胰蛋白酶缺乏症[111,112]
- 肺静脉闭塞性疾病[113]
- 多发性肌炎相关的间质性肺病[114]

一些小型病例系列研究显示，尤其是肺结节病有较高的病理复发率[115]。肺结节病通常是因为在肺活检标本上发现非干酪样肉芽肿而被偶然发现，但这些病理复发未对结局产生不利影响[88,91]。

因为肺移植后的生存期相对基础疾病的自然病程来说是短暂的，所以未来很可能在长期生存患者中出现其他疾病复发。

移植物抗宿主病

移植物抗宿主病(graft-versus-host disease, GVHD)是有活性的供者淋巴细胞攻击受者组织所致，临床表现为皮肤、肝脏、胃肠道和骨髓的功能障碍(　表 1)。GVHD通常发生在造血干细胞移植后，是肺移植的一种罕见并发症[116-118]。(参见 “移植物抗宿主病的发病机制”)

GVHD的临床表现包括皮肤斑丘疹、重度血细胞减少(特别是中性粒细胞减少)、淤胆性肝炎、胃肠炎和发热[116,119,120]。临床表现可提示GVHD的诊断，但重度药物反应也可能导致相似表现。可通过皮肤活检及外周血嵌合体检测确诊，后者可量化供者和受者来源的循环淋巴细胞的百分比。GVHD在肺移植受者中尽管罕见，但死亡率似乎极高[116]。(参见 “急性移植物抗宿主病的临床表现、诊断和分级”和 “急性移植物抗宿主病的预防”)

尚不确定肺移植后GVHD的危险因素。有理论认为，受者细胞介导性免疫监测功能严重受损可能有利于供者源性免疫细胞的存活。据报道，一名患者有端粒酶逆转录酶(telomerase reverse transcriptase, TERT)基因功能丧失性突变相关的肺纤维化，在肺移植后出现了急性GVHD[121]。TERT基因突变可导致免疫功能受损。(参见 “特发性肺纤维化的发病机制”，关于‘端粒酶基因’一节)

药物引起的肺毒性

免疫抑制剂引起的肺毒性是一种不常见的副作用，但是当肺移植受者出现呼吸困难、血氧饱和度下降及X线摄影发现阴影时，需考虑这种情况。例如，肺毒性偶尔与使用雷帕霉素机能靶点(mechanistic target of rapamycin, mTOR；以前称哺乳动物雷帕霉素靶蛋白)抑制剂相关，如西罗莫司或依维莫司。其发病机制尚不清楚，而且毒性反应并不明确取决于药物血清水平[122,123]。

症状通常在启动mTOR治疗后6个月内出现，不过6个月后出现症状的情况也有报道。患者常表现为干咳、进行性呼吸困难、疲劳和无力。也可能出现发热和咯血[124]。X线摄影异常包括双肺间质阴影、肺泡实变和结节状影，停药后可持续数月[123,125,126]。支气管肺泡灌洗(bronchoalveolar lavage, BAL)液分析可发现淋巴细胞性肺泡炎，以及更为少见的肺泡出血。组织学表现包括机化性肺炎[也称闭塞性细支气管炎伴机化性肺炎(bronchiolitis obliterans organizing pneumonia, BOOP)]、肺间质淋巴细胞浸润，以及有时发生的肺泡出血[123,124,127]。mTOR抑制剂相关肺毒性有可能逆转(特别是早期发现时)，因此在肺功能减退的鉴别诊断中务必考虑此情况[128]。mTOR抑制剂也可能增加VTE的发生风险，因此对于新发呼吸困难或低氧血症的患者，应考虑肺栓塞的诊断[29]。(参见“抗肿瘤药物的肺毒性：分子靶向药物”，关于‘雷帕霉素及其类似物’一节)

肺外并发症

高氨血症 — 报道显示，重度高氨血症是移植术后早期、罕见但常常致死的昏迷病因，累及1%-4%的肺移植受者[129-133]。除了肝功能衰竭或尿素循环酶缺乏外，人型支原体(*Mycoplasma hominis*)或脲原体(*Ureaplasma*)引起的全身性感染也是肺移植受者中高氨血症的特有病因。这些微生物可代谢尿素作为能量来源，并产生氨等副产品。治疗这些患者的高氨血症时，需立即启用抗上述微生物的药物。(参见“人型支原体与脲原体感染”和“成人肝性脑病的临床表现及诊断”，关于‘氨’一节)

下列研究阐述了支原体(*Mycoplasma*)或脲原体在高氨血症中的作用。一项病例报道发现，一例伴致死性高氨血症的肺移植受者的血液及多种组织(气管、肺、小肠和结肠)中有人型支原体感染[134]。随后一项研究在并发高氨血症综合征的肺移植受者中发现了解脲脲原体(*Ureaplasma urealyticum*)或微小脲原体(*U. parvum*)感染，但在20例血氨浓度正常的肺移植受者中均未检出这些微生物[132]。对高氨血症综合征患者给予抗脲原体抗菌药物治疗，疾病出现了生化和临床缓解。目前仍不清楚移植术后出现此疾病的原因。

如果肺移植受者出现与高氨血症相符的临床表现(如，不明原因的嗜睡、激越或痫性发作)，应测量血清氨水平。如果血氨增高，应对血或血浆和BAL样本进行PCR检测和培养，以筛查支原体和脲原体。(参见“人型支原体与脲原体感染”，关于‘诊断’一节)

在等待培养和PCR结果的同时，应启动抗人型支原体和脲原体的经验性治疗。人型支原体通常对四环素类抗生素敏感，脲原体通常对大环内酯类、氟喹诺酮类及四环素类抗生素敏感。鉴于耐药微生物有可能一开始便存在或在治疗中出现，应进行抗菌药物联合治疗[132]。抗生素治疗见其他专题。(参见“人型支原体与脲原体感染”，关于‘脲原体’一节)

其他一些干预措施也可能有益，比如去除饮食中的外源性氮，血液透析以清除血流中的氨，以及给予静脉用苯甲酸钠和苯乙酸钠替代尿素来参与含氮废物的排泄[135-137]。有报道称，一名患者实施了脑内引流以治疗脑水肿[135]。(参见“间歇性透析和连续性血液净化模式在高氨血症患者中的应用”)

心脏并发症 — 肺移植后可能发生几种类型的心脏并发症。早期发现并立即治疗对于改善患者结局至关重要。

- **房性心律失常**—房性心律失常在肺移植术等心胸部手术后相当常见。房性心律失常(心房颤动最常见)在术后早期的发病率为25%-35%[138-142]。危险因素包括：高龄、男性、左心房肥大、既往心房颤动、IPF、心瓣膜关闭不全、冠状动脉疾病、既往冠状动脉旁路移植术、心脏舒张功能障碍和应用体外循环[138-140,142-144]。

  供肺左心房断端/肺静脉与受者左心房间的手术吻合口似乎是出现心房扑动大折返环路的一个重要部位[145]。房性心律失常一般经常规治疗可缓解，如抗心律失常药和心脏复律。但该并发症仍可导致住院时间延长和死亡率增加[139]。通常可在肺移植后2-3个月内停用药物，复发风险较低。研究显示，在肺移植术后晚期，心房扑动和房性心动过速较常见，而心房颤动的风险较低[139,146]。

- **血流动力学不稳**—移植后立即出现低血压相当常见，合理应用血容量补充、血管加压药和正性肌力药后通常能明显缓解。以下情况均可造成心肌损伤：术中冠状动脉空气栓塞，术中心脏操作，术后来自左心房肺静脉吻合口的小栓子栓塞冠状动脉，或已有冠状动脉疾病引起的梗死；但导致左心室功能不全或两心室功能衰竭的有临床意义的心肌损伤并不常见。相比之下，术前诊断出重度肺动脉高压与致命性血流动力学不稳的风险增加有关。重度右心室功能不全、应用体外循环(伴随有出血风险增加)及早期移植物破坏的发病率增加可促成该风险[147]。

- **冠状动脉疾病**—长远来看，许多肺移植受者都会出现冠状动脉疾病的危险因素[33]。在国际心脏与肺移植协会登记中心的5年生存者中，危险因素的发生率非常高：体循环高血压82%，高脂血症59%，肾功能不全55%(3%需要透析)，糖尿病40%。一项单中心回顾性研究纳入了126例移植前没有高血压、高胆固醇血症和糖尿病的肺移植受者，术后3年内有90%的受者出现了至少1种心血管疾病危险因素[148]。其中多数危险因素与移植后免疫抑制药物直接或间接相关。因此，这些危险因素从某种程度上来说不可避免，但仍应通过标准的饮食调整、锻炼及药物治疗尽可能加以控制。以下发现可能出乎意外，一项研究比较了伴或不伴轻中度无症状冠状动脉疾病的肺移植受者(术前和术中都未行血运重建)，在伴冠状动脉疾病的受者中，术后病情进展到需要干预的风险为6%[149]。高龄、心房颤动和诊断出IPF是术后心脏事件的独立预测指标。

- **心包炎**—一些病例报道发现，双肺移植受者在术后6个月-9年出现了缩窄性心包炎[150-154]。患者通常表现为呼吸困难、端坐呼吸和下肢水肿。必须排查心包炎的感染性和恶性病因[153,155-157]。治疗通常采用心包切除术[154]。缩窄性心包炎的诊断和治疗见其他专题。(参见 “缩窄性心包炎”)

糖尿病 — 在肺移植受者中，术后第1年新发糖尿病的发生率为20%左右，术后第5年为30%以上[33,148,158-160]。移植术后糖尿病(post-transplantation diabetes mellitus, PTDM)的危险因素包括：使用糖皮质激素和钙调磷酸酶抑制剂、高龄、肥胖(BMI>30)和患有CF[160,161]。他克莫司治疗患者比环孢素治疗患者发生糖尿病的可能性更大，但葡萄糖不耐受不被视作将他克莫司改为环孢素的原因。患有糖尿病与肺移植受者的死亡风险增加有关[160,162-164]。针对PTDM评估和治疗的国际共识性指南见其他专题[165]。(参见 “成人肾移植后的糖尿病”)

肾功能不全 — 急性肾衰竭(acute renal failure, ARF)在肺移植术后常见[166-169]。一项回顾性分析显示，657例肺移植受者中有424例在术后最初2周有过至少1次急性肾损伤(acute kidney injury, AKI)发作[166]。在一项来自加拿大亚伯达大学的研究中，69%的肺移植受者在术后早期出现了AKI[170]。另一项研究显示，296例连续肺移植受者中有166例(56%)出现了急性肾功能不全，但仅有8%的患者需要透析[167]。出现需要肾脏替代治疗(renal replacement therapy, RRT)的ARF与早期死亡风险增加有关。移植后重度ARF的独立预测指标包括：术前诊断出肺高压和IPF，基线肾小球滤过率(glomerular filtration rate, GFR)降低，机械通气>24小时，给予静脉用两性霉素B。一项针对肺移植后ARF的经验证风险评分包含了如下因素：人种、诊断、BMI、糖尿病、术前GFR、移植前入住ICU/ECMO和其他因素[171]。患者出现需RRT治疗的AKI是死亡的危险因素[170,172]。

据报道，肺移植受者的慢性肾脏病(chronic kidney disease, CKD)发生风险为术后3年内5%，术后6年约为15%[173]；若采用更低CKD诊断阈值[GFR<60mL/(min·1.73m^2)]，则估计值更高(术后5年为68%)。国际心肺移植协会登记中心的结果显示，15%的肺移植受者在术后第5年肌酐大于2.5mg/dL[174]。慢性肾衰竭也与死亡率增加相关[173,175]。根据研究与患者群体的不同，慢性肾功能不全所涉及的危险因素包括：高龄、吸烟史[175,176]、女性性别、早期ARF、使用钙调磷酸酶抑制剂和其他肾毒性药物、高血压、结节病和糖尿病[177-179]。用于估算GFR的公式是肺移植后CKD发生风险的最佳预测指标[179,180]。移植后肾毒性的危险因素、预防和治疗见其他专题。(参见 “肾功能的评估”，关于‘估算方程’一节和 “肾功能与非肾脏实体器官移植”，关于‘肺移植’一节和 “肾功能与非肾脏实体器官移植”，关于‘预防和治疗策略’一节和 “环孢素和他克莫司的肾毒性”，关于‘发病率’一节)

肠壁积气和气腹 — 肠壁积气(pneumatosis intestinalis, PI)是指在小肠或大肠的肠壁内积存气体。一项单中心研究报道，在11年内，373例连续肺移植受者中有11例发生了肠壁积气。结局基本良好(短期生存率100%)，不过其中2例出现了高乳酸盐水平，需要肠道切除[181]。虽然有报道称肠壁积气的危险因素包括糖皮质激素治疗、感染性结肠炎和脓毒症，但在无症状患者中肠壁积气也可能是良性表现。在一项纳入321例双肺移植的病例系列研究中，影像学检查发现7例无症状的患者存在肠壁积气和/或气腹[182]；6例患者有肠壁积气，其中3例同时还有气腹。未发现这些表现的明确原因，X线摄影表现在平均24日后自行消失。(参见 “肠壁积气”)

神经系统并发症 — 神经系统并发症在肺移植后常见，一项为期10年的队列研究显示，92%的患者出现神经系统并发症，重度神经系统并发症的发生率为53%[183,184]。在该研究中，高龄是神经系统并发症的重要预测指标。脑病最常见，且最常出现在术后早期。

据报道，5%-10%的肺移植受者发生脑卒中[183-186]。脑卒中发病机制方面，除了公认的动脉粥样硬化血栓形成机制，还必须考虑肺移植受者所特有的2种栓塞机制。其一是血管吻合完成后未能完全清除肺血管树和心腔内的空气，这可导致肺再灌注后立即出现或术后早期出现空气栓塞。此外，左心房吻合口处的血栓形成可导致移植后数日至数周出现栓塞性脑卒中。(参见上文‘血管吻合口并发症’)

如果临床和放射影像学表现提示有多个脑梗死区，应立即进行经食管超声心动图检查。如果证实有血栓，应在排除其他禁忌证后启动全身抗凝治疗。(参见上文‘肺静脉血栓形成’)

其他并发症 — 肺移植受者还可能会发生许多其他内科和外科问题。其中多数问题并非肺移植所特有，而是免疫抑制剂的副作用，或者是可被移植后方案加重的一般躯体问题[55,187]。

主要的问题包括：

- 骨质疏松[187-191]。(参见 “实体器官移植或干细胞移植后的骨质疏松”)
- 肥胖[192-194]。
- 贫血[80]。
- 胃轻瘫和胃食管反流病(gastroesophageal reflux disease, GERD)[195]。(参见 “肺移植后的生理变化”，关于‘口咽性吞咽困难、胃食管反流和胃轻瘫’一节)
- 高胆固醇血症和高甘油三酯血症[148,174]。据报道，肺移植受者术后5年内高脂血症的发生率为59%[174]。(参见 “成人肾移植后血脂异常”)
- 胆囊炎、憩室炎、胃肠道穿孔和胰腺炎[196,197]。
- CF患者中的远端肠梗阻综合征–远端肠梗阻综合征(distal intestinal obstruction syndrome, DIOS)以前称“胎粪性肠梗阻等危症”，其特征是肠内容物造成回盲肠急性完全或部分阻塞，可能在肺移植后更常发生[198,199]。(参见 “囊性纤维化：消化系统疾病概述”，关于‘远端肠梗阻综合征’一节)
- 呼吸肌和肢体肌无力。(参见 “肺移植后的生理变化”，关于‘呼吸肌和骨骼肌功能’一节)

总结与推荐

- 急慢性肺移植排斥反应、气道吻合口问题、胸腔并发症和原发性移植肺功能丧失等肺移植相关并发症见其他专题。(参见 “急性肺移植排斥反应的评估和治疗”和 “抗体介导肺移植排斥反应的评估和治疗”和 “慢性肺移植物功能丧失：闭塞性细支气管炎”和 “肺移植后气道并发症”和 “肺移植术的胸膜并发症”和 “Primary lung graft dysfunction”)
- 肺动静脉/左心房吻合口并发症(如血栓形成、血管狭窄和动脉扭曲)较气道吻合口并发症少见，但可能产生毁灭性影响。(参见上文‘血管吻合口并发症’)
- 3%-9%的肺移植受者并发膈神经损伤造成的膈肌功能障碍。如果患者术后出现呼吸困难、低氧血症、通气不足、肺不张，直立位胸片示双侧或单侧膈肌抬高和/或难以撤掉呼吸机，应怀疑膈肌麻痹。(参见上文‘膈神经和膈肌功能障碍’和 “成人单侧膈肌麻痹与膈膨出的病因和诊断”和 “双侧膈肌麻痹的病因与诊断”和 “膈肌麻痹的治疗”)
- 肺移植受者发生静脉血栓栓塞症(VTE)的风险增加。当肺移植受者出现呼吸困难、低氧血症或运动诱导去氧饱和时，应高度怀疑VTE。(参见上文‘静脉血栓栓塞症’)

- 肺移植受者发生恶性肿瘤的风险增加。吸烟有关的肺部疾病是肺移植的常见指征，因此约2%的单肺移植受者自体肺发生肺癌。总体上，肺移植受者的肺癌发生风险是一般人群的5.5倍。(参见上文'恶性肿瘤')

- 肺移植受者中移植术后淋巴细胞增生性疾病(PTLD)的发生率约为5%，但在术前EB病毒血清阴性而术后发生原发性EB病毒感染的肺移植受者中明显高得多。值得注意的是，与EB病毒感染无关的PTLD的发病率正在增加。PTLD的临床表现因移植术后的时间而异，胸腔内或移植肺受累更常见于术后第1年内发病的病例，而胸腔外表现更常见于之后发病的病例(参见上文'移植术后淋巴细胞增生性疾病'和 "移植后淋巴增殖性疾病的流行病学、临床表现和诊断"和 "移植后淋巴增殖性疾病的治疗和预防")。

- 据报道一些疾病可在移植肺中复发，包括结节病、淋巴管平滑肌瘤病、弥漫性泛细支气管炎、肺泡蛋白沉积症、脱屑型间质性肺炎、肺朗格汉斯细胞组织细胞增生症、细支气管肺泡癌和特发性肺含铁血黄素沉着症。(参见上文'原发疾病复发')

- 移植物抗宿主病(GVHD)的病因是来自移植肺的有活性供者淋巴细胞攻击受者组织(如皮肤、胃肠道、肝脏和骨髓)，是肺移植的罕见并发症。(参见上文'移植物抗宿主病')

- 免疫抑制剂(如西罗莫司和麦考酚酯)引起的肺毒性虽然是肺移植后的少见不良反应，但当肺移植受者发生呼吸困难、血氧饱和度下降和X线摄影发现阴影时，需要予以考虑。(参见上文'药物引起的肺毒性')

- 肺移植受者有可能因免疫抑制剂的不良反应或基础疾病而发生其他并发症，包括高氨血症、房性心律失常、血流动力学不稳、冠状动脉疾病、糖尿病、肾功能不全、肠壁积气和脑卒中。(参见上文'肺外并发症')

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图表

Grading of acute graft-versus-host disease

Organ	Stage	Description
Skin	1	Maculopapular rash over <25% of body area
	2	Maculopapular rash over 25 to 50% of body area
	3	Generalized erythroderma
	4	Generalized erythroderma with bullous formation and often with desquamation
Liver	1	Bilirubin 2.0 to 3.0 mg/dL
	2	Bilirubin 3.1 to 6.0 mg/dL
	3	Bilirubin 6.1 to 15.0 mg/dL
	4	Bilirubin >15.0 mg/dL
Gut	1	Diarrhea >30 mL/kg or >500 mL/day
	2	Diarrhea >60 mL/kg or >1000 mL/day
	3	Diarrhea >90 mL/kg or >1500 mL/day
	4	Diarrhea >90 mL/kg or >2000 mL/day; or severe abdominal pain with or without ileus
Glucksberg grade		
I – Stage 1 or 2 skin involvement; no liver or gut involvement; ECOG PS 0		
II – Stage 1 to 3 skin involvement; Grade 1 liver or gut involvement; ECOG PS 1		
III – Stage 2 or 3 skin, liver, or gut involvement; ECOG PS 2		
IV – Stage 1 to 4 skin involvement; Stage 2 to 4 liver or gut involvement; ECOG PS 3		
International Bone Marrow Transplant Registry Severity Index		
A – Stage 1 skin involvement; no liver or gut involvement		
B – Stage 2 skin involvement; Stage 1 to 2 gut or liver involvement		
C – Stage 3 skin, liver, or gut involvement		
D – Stage 4 skin, liver, or gut involvement		

ECOG: Eastern Cooperative Oncology Group; PS: performance status.

Graphic 68233 Version 8.0

Contributor Disclosures

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利益矛盾的解决方案

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