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高龄合并2型糖尿病结直肠癌患者预后预测指标分析

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摘　要

结直肠癌是最常见的恶性肿瘤之一，近年来，随着生活水平的提升，高龄患者逐步增多，我国人口调查显示老年人群预计将占据世界人口的22%的比例，因此未来将有更多的高龄结直肠癌患者，而高龄患者常患有一些基础疾病，如心血管相关疾病、肺部疾病，以及近年老年糖尿病患者比例的增加，使得共患2型糖尿病的高龄结直肠癌患者在未来社会中占很大的比重。此外，有研究证实糖尿病与结直肠癌的发展密切相关，特别是在老年人中。而手术依然是治疗结直肠癌的主要手段。此类患者能否行手术治疗？手术是否安全？因此我们有必要对高龄且合并2型糖尿病患者的研究现状进行整理，找到可以代表高龄和2型糖尿病相关的预测指标，建立预测模型，一方面可以评估能否手术，另一方面，可以根据预测结果提前采取干预手段以减少术后不良结局。这篇综述中，讨论了与高龄和2型糖尿病的相关指标及未来展望。

关键词

结直肠癌，2型糖尿病，老年人，衰弱指数

Analysis on Prognostic Predictors of Elderly Colorectal Cancer Patients Combined with Type 2 Diabetes Mellitus

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Abstract

Colorectal cancer is one of the most common malignant tumours. In recent years, with the improvement of living standards, the number of elderly patients has gradually increased, and China's population survey shows that the elderly population is expected to occupy 22% of the world's population, so there will be more elderly colorectal cancer patients in the future, and elderly patients often suffer from some underlying diseases, such as cardiovascular-related diseases and lung diseases, as well as the proportion of elderly diabetics in recent years. The increase in the proportion of older patients with diabetes mellitus in recent years has led to a large proportion of older colorectal cancer patients with type 2 diabetes mellitus in society in the future. In addition, studies have confirmed a strong association between diabetes and the development of colorectal cancer, particularly in the elderly. Surgery remains the mainstay of treatment for colorectal cancer. Can these patients be treated surgically? Is surgery safe? It is therefore necessary to collate the current state of research on the elderly with type 2 diabetes, to find predictors that represent the association between elderly patients and type 2 diabetes, and to develop predictive models that can, on the one hand, assess the possibility of surgery and, on the other hand, allow for early interventions to reduce adverse postoperative outcomes based on the predictive results. In this review, indicators associated with elderly patients and type 2 diabetes are discussed and future perspectives are provided.

Keywords

Colorectal Cancer, Type 2 Diabetes Mellitus, The Elderly, Frailty Index

1. 引言

结直肠癌(colorectal cancer, CRC)是最常见的恶性消化系统肿瘤之一[1]。流行病学调查预计，到 2030 年全球结直肠癌的新发生病例数将会超过 220 万，到 2050 年死亡患者数将会超过 110 万[2]。随着预期寿命的增加，80 岁以上高龄结直肠癌患者将占很大比例，该类人群伴有合并症的比例达到 53% [3]。外科手术仍然是治疗结直肠癌的主要治疗方式，但高龄患者一般被视为高风险的手术人群，因为他们更可能有紧急情况以及伴有基础疾病[4]。高龄患者的围术期可能需要更加严格的规范化管理，同时传统的预后指标可能不适用于 80 岁以上的高龄结直肠癌患者[5] [6]。

近年来，我国 2 型糖尿病(type 2 diabetes mellitus, T2DM)患者呈上升趋势，且结直肠癌与 T2DM 存在相同的危险因素，如摄食高热量、高脂饮食，肥胖和运动量缺乏等[7]。当前研究认为，糖尿病与结直肠癌发病率呈正相关且糖尿病影响结直肠癌患者预后。一项纳入 50 万人的前瞻性队列研究表明，糖尿病患者更易患结直肠癌[8]；此外，Zhu B [9]等进行的一项荟萃分析表明，与未患糖尿病者相比，糖尿病患者在结直肠癌中的生存期缩短了 5 年，总体生存率降低了 17%。但是也有研究说明糖尿病本身并不是影响结直肠癌术后生存的影响因素，而是糖尿病的相关并发症，以及糖尿病病程[10]。糖尿病相关指标对于结直肠癌的危险程度评估尚未达成共识。而未来社会中将出现更多的高龄且合并 2 型糖尿病的结直肠癌患者。但目前对于如何治疗此类患者仍然缺乏共识。所以我们有必要对该类患者发病机制、围术期管理及

预后情况分析了解，并找到高龄合并 2 型糖尿病的结直肠癌患者相关的预测指标，提前发现潜在的风险并了解预后，提前进行干预，从而可以减少术后相关并发症以及不良结局的发生。

2. 2 型糖尿病患者与结直肠癌

2.1. T2DM 与 CRC 的相关性

国内外相关研究显示[11] [12] [13]，T2DM 是结直肠癌的独立危险因素。有一些研究报道糖尿病与结直肠癌的相关性与糖尿病的病程相关，但当糖尿病病程超过 12 年后，两者就无显著关系[14] [15] [16]。一项澳大利亚的研究发现糖尿病会增加手术相关并发症，但对非手术相关并发症、重返手术室、30 天内死亡或 30 天内再次住院没有显著影响，后对糖尿病患者按照有无糖尿病相关并发症分层分析发现有糖尿病相关并发症的患者 30 天死亡率(OR 13.7, 95% CI 3.4~54.7)和住院时间延长 3.8 天(95% CI 0.7~7.1) [17]，以及术后并发症增加的趋势(OR 1.7, 95% CI 1.0~3.8)，从而说明了糖尿病本身对结直肠癌无影响，糖尿病相关并发症与结直肠癌预后相关。糖尿病患者体内高水平的胰岛素和血糖会促进肿瘤生长因子的表达，并为肿瘤生长提供能量。氧化应激和 DNA 损伤是肿瘤发展的主要诱因，而高血糖在此过程中发挥了诱导剂的作用[18]。糖尿病中诱发结直肠癌发病的相关影响因素如下：

2.2. 胰岛素抵抗与高胰岛素血症

2 型糖尿病存在胰岛素抵抗和高胰岛素血症。胰岛素样生长因子(insulin-like growth factor, IGF)促进癌细胞的增殖、分化，抑制细胞凋亡，与癌症发展密切相关。Yap R [19]等的高胰岛素血症学说认为在结直肠癌的发展过程中，由胰岛素抵抗作用所致的高胰岛素血症起到了重要作用。Mangiapane 等[20]在小鼠模型中发现，高胰岛素血会使得 IGF-1 的表达活性增强，从而增加肿瘤细胞的增殖与侵袭。IGF-1 在许多恶性肿瘤的进展过程中存在，通常 IGF-1 的异常增多在结直肠癌的发病过程当中也具有重要影响[21]。有研究发现胰岛素结合蛋白-3 (IGFBP-3)也对肿瘤的进展起到促进作用，并且还能够增加游离 IGF-1 [22]。因此，检测血浆 IGF-1 和 IGFBP-3 的水平对于预测糖尿病患者结直肠癌的发病率有重要意义。

2.3. 高血糖对肿瘤细胞的作用

糖化血红蛋白会增加癌症发生的风险[23]。肿瘤细胞需要通过葡萄糖摄取维持自身增殖。研究发现，糖尿病会增加结直肠癌患者的死亡风险，且这种相关性与血糖浓度呈正相关[24]。Masur 等发现，高浓度葡萄糖和胰岛素对 HT29、HW480、MCF-7、MDAMB468、PC3 和 T24 等癌细胞系有明显的促增殖作用，并证明高浓度蒲萄萄会增加肿瘤的迁移速率，而迁移活性的增加是激活 PI3K、PKCx、MLCK 所介导的[25]。Detarya M 等认为[26]，高血糖作用机制是通过激活 STAT 3 及其下游靶基因 CyclinD1、Vimentin、MMP2 来实现的。另外，Garary-Sevilla 等[27]发现，高血糖有助于诱导活性氧(reactive oxygen species, ROS)的异常蓄积以及产生晚期糖基化终末产物(advanced glycation end products, AGEs)增多，导致 DNA 损伤、突变，促进上皮细胞转化为肿瘤细胞。Her TK 等人研究表明[28]，与正常组织相比，癌症患者的葡萄糖摄取量显著增加，因此高血糖会导致糖尿病患者增加罹患癌症的风险，高血糖会增强癌细胞的迁移能力和黏附力，促进癌细胞相关基因的表达。

2.3. 慢性炎症

大量研究表明，肥胖是多种癌症的危险因素，包括食管癌、胰腺癌、结直肠癌和乳腺癌，肥胖人群由于脂肪组织的异常分泌常伴随慢性炎症，这可能是致癌的危险因素[29]。脂肪组织分泌的细胞因子可分为脂肪组织特异表达的脂肪因子如瘦素、脂联素和非特异表达的脂肪因子如多种炎症因子，而瘦素介导

的 PI3K、MAPK、信号转导和转录激活因子信号通路被激活，从而抑制细胞凋亡、诱导血管生成和促进有丝分裂，与肿瘤发展相关[30]。Valencia 等发现[31]，肥胖患者体内过多的脂肪组织发生炎症反应会导致促炎细胞因子的产生，如肿瘤坏死因子 α (Tumor necrosis factor-α, TNF-α)和白细胞介素 6 (Interleukin-6, IL-6)含量增加，炎症因子有利于建立适宜肿瘤生长的微环境。Tanaka M 等[32]发现，肥胖患者的脂肪组织中巨噬细胞的堆积是全身性炎症的关键，因为脂肪组织中的巨噬细胞会产生大量的 TNF-α 和 IL-6。

2.4. 氧化应激

氧化应激是与糖尿病和癌症发生紧密相关的另一个关键因素。Ceriello [33]发现，在糖尿病患者中，生物标志物的水平和氧化应激往往明显增加。氧化应激最主要的作用是导致 DNA 的突变。Valko 等[34]研究发现，DNA 突变在癌变进程中发挥关键作用，高血糖能够刺激线粒体电子传递链中的超氧化物[35]。高胰岛素血症可能增加氧化应激[36]，氧化应激会干扰许多基因以及正常信号通路表达，这些途径都利于癌细胞的产生[37]。已有研究证明 TNF-α 介导激活 NF-κB 是影响结直肠癌进展的通路，而 ROS 已被认为是细胞因子依赖性激活 NF-κB 的第二信使[38]，所以氧化应激在糖尿病促进癌症进展过程中起重要影响。

3. 高龄与直肠癌的相关性

随着老龄化的不断进展，高龄患者在全球所占比例逐步上升[39] [40]，随着年龄的增长，老年人身体机能下降，新陈代谢减慢，代偿能力降低，在某些情况下，还有各种慢性疾病，这些都使麻醉和手术具有风险，术后容易出现并发症，甚至死亡，所以对于高龄患者的治疗策略明显不同。老年患者的术前预处理评估对于临床治疗方案的选择和术后并发症的预测很重要[41] [42]。传统的评估系统只对患者某项指标进行评估，难以全面了解老年患者的身体健康状况。文献报道，国外社区老年人衰弱平均发生率为 10.7% [43]，中国部分地区衰弱发生率为 6.8%~14.9% [44]。北京协和医院一项关于中国 65 岁以上患者结果显示老年患者衰弱发生率为 48.7%。有研究结果显示衰弱与营养不良存在关联，报道称这可能与激素、代谢、维生素 D 水平、重要器官功能储备减少等相关[45]。总之，了解老年患者的衰弱相关指标可以帮助预测潜在风险和预后。有研究报道营养不良、运动及日常生活能力、慢性疾病和炎症因子都会影响衰弱。

4. 高龄评估指标

4.1. 衰弱

国内已经关注老年综合评估多年，通过借助老年综合评估工具可及早全面评估老年患者一般状况。明显改善老年患者生活质量。对于老年患者全面评估重要脏器功能状况、明确患者的医疗和护理需求、制定可行的治疗干预措施[45] [46]。Fried 衰弱表型(frailty phenotype, FP)：是目前比较全面且在临床工作中常用的衰弱评估工具[47]。近年还有研究表明使用老年营养风险指数可更好地评估老年患者营养状况[48]，指导改善老年营养不良水平。营养风险筛查量表-2002 (nutritional risk screening-2002, NRS-2002)：适用于住院患者营养风险筛查，简便易于操作，可预测临床结局。有研究发现类肿瘤坏死因子(TNF-like weak inducer of apoptosis, TWEAK)是肌少症的独立预测因素，会刺激细胞凋亡和诱导肌损伤和萎缩[49]。高水平的 TWEAK 对衰弱和死亡结局有一定的预测价值。

4.2. 衰弱模型

老年综合评估(comprehensive geriatric assessment, CGA)是常用的一种评估模型[50]，其中衰弱指数模型的建立会在一定程度上把老年患者的综合情况量化起来，但在老年肿瘤患者应用较少。近年来基于 CGA 体系构建的衰弱指数(frailty index, FI-CGA)模型得到重视。但此评估对于手术患者的针对性不强[51]。

最近提出用改良衰弱指数(modified frailty index, mFI)来量化接受手术的老年人的虚弱程度，与年龄相比，mFI 侧重于术前指标，是一种多维度的综合健康评估方法，通过快速计算，从病史和体检中收集数据，可以更全面、快速、系统地了解老年人的身体健康状况，并能预测住院时间和预后情况[52]。已经有研究结果显示[53]，mFI 和胃肠道术后并发症和术后 30 d 内病死率密切相关。美国最新研究表明[54]，mFI 是预测胃肠癌患者术后并发症的重要因素。

mFI 可以为老年患者的衰弱程度提供了一个具体标准，并用于术前的风险分层，为老年结直肠癌手术提供更加具体的身体状态评估分数，及时干预，减少老年术后相关并发症及不良事件的发生。在日常临床治疗中，衰弱以及其相关因素，如营养不良等，是可以防治和逆转的[55]。因此将 mFI 纳入老年结直肠癌患者临床评估体系可以为改善患者的预后做出贡献。

同时，老年患者被多种慢性病困扰，随着步入高龄，罹患肿瘤，焦虑、抑郁心理突出，给住院治疗过程带来阻碍，结合老年心理评估的自评量表(geriatric depression scale, GDS)老年抑郁量表，或 PHQ-9 他评量表来评估老年患者心理状况[56]。通过多维度的评估情况汇总计算，可较好细化评价老年肿瘤患者生存质量。

5. 小结和展望

近年来，我国经济不断快速发展，人民生活水平也得到了不断地提升，高糖高脂饮食已普遍成为当前人们的饮食方式和习惯。但与此同时糖尿病的发病率也呈现出了明显的上升趋势，老年人以 2 型糖尿病为著，糖尿病可出现多种并发症，严重影响患者的生活质量。而 2 型糖尿病的长期患者常常并发结直肠癌。评估高龄患者对手术的耐受程度以及出现术后并发症的风险是临床上亟待解决的问题。高龄患者由于身体各项机能的衰退，身体代偿能力较年轻患者整体下降并且常伴有慢性消耗性疾病，所以较年轻患者相比，高龄患者的手术耐受性一般较差。这些问题都在一定程度上增加了高龄患者接受手术的风险，这类患者更加容易在术后出现相关并发症，甚至出现死亡。所以提前对老年患者的具体健康状况进行综合评估有利于提前预测患者术后结局。因此我们通过寻找 2 型糖尿病的相关指标与老年患者的相关指标，预测此类患者的预后将特别有意义。

高龄且合并 2 型糖尿病的结直肠癌患者，除评估病情及身体状况外，注重管理和调控围术期，手术依然是第一选择。特别注意的是，长期控制血糖在合理范围内，以及预防产生糖尿病相关并发症是取得术后良好结局的关键。因此，对于高龄且合并糖尿病的患者一定要在术前合理评估身体状况，围术期严密监测并调控血糖。仍有以下问题需要解决：目前大多数流行病学研究主要集中在单纯合并糖尿病的结直肠癌患者或者单纯老年结直肠癌患者，但对于高龄和糖尿病共同作用下的结直肠癌患者手术是否安全？能否进行手术？术后结局如何？尚需进一步的多中心、大样本的队列研究。找到与合并糖尿病结直肠癌相关的生物标志物并联合基于老年综合评估(CGA)体系构建的衰弱指数模型，从而提前制定规避高龄合并糖尿病的结直肠癌的潜在风险的策略，并通过多学科合作的方式对此类患者进行个性化指导管理，有助于为高龄合并糖尿病的结直肠癌患者提供更加合理的治疗决策。

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