

· 论 著 ·

宁波市肺结核患者药物性肝损伤的影响因素研究

杨天池¹, 李舒婷², 陈琴³, 陈同¹, 车洋¹1. 宁波市疾病预防控制中心结核病防治所, 浙江 宁波 315010; 2. 宁波大学, 浙江 宁波 315211;
3. 中国科学院大学宁波华美医院, 浙江 宁波 315010

摘要: **目的** 分析2015—2019年宁波市肺结核患者药物性肝损伤的影响因素, 为预防药物性肝损伤提供依据。**方法** 通过中国疾病预防控制中心结核病管理信息系统和宁波市区域诊疗信息平台收集2015—2019年宁波市肺结核患者人口学资料、药物性肝损伤发生情况和抗结核药物治疗前疾病史等资料。采用多因素logistic回归模型分析药物性肝损伤的影响因素。**结果** 纳入肺结核患者9 397例, 男性6 242例, 占66.43%; <60岁6 192例, 占65.89%; 初治8 678例, 占92.35%。发生药物性肝损伤1 425例, 发生率为15.16%。肝损伤1级729例, 占51.16%; 2级24例, 占1.68%; 3级7例, 占0.49%; 4级7例, 占0.49%; 未分级658例, 占46.18%。药物性肝损伤发生间隔时间的 $M(Q_R)$ 为24(44)d。多因素logistic回归分析结果显示, 初治($OR=1.464$, $95\%CI: 1.153 \sim 1.859$)和肝病史($OR=2.001$, $95\%CI: 1.709 \sim 2.342$)是肺结核患者药物性肝损伤的危险因素。**结论** 2015—2019年宁波市肺结核患者药物性肝损伤发生率为15.16%, 初治和肝病史与药物性肝损伤有关。

关键词: 肺结核; 药物性肝损伤; 影响因素

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Influencing factors for drug-induced liver injury among patients with pulmonary tuberculosis in Ningbo City

YANG Tianchi¹, LI Shuting², CHEN Qin³, CHEN Tong¹, CHE Yang¹

1. Department of Tuberculosis Control and Prevention, Ningbo Center for Disease Control and Prevention, Ningbo, Zhejiang 315010, China; 2. Ningbo University, Ningbo, Zhejiang 315211, China; 3. Ningbo Hua Mei Hospital, University of Chinese Academy of Sciences, Ningbo, Zhejiang 315010, China

Abstract: Objective To investigate the factors affecting drug-induced liver injury among patients with pulmonary tuberculosis in Ningbo City from 2015 to 2019, so as to provide insights into the prevention of drug-induced liver injury. **Methods** Demographic features, presence of drug-induced liver injury, and disease history prior to anti-tuberculosis therapy were captured from patients with pulmonary tuberculosis in Ningbo City from 2015 to 2019 through the Tuberculosis Management Information System of the Chinese Disease Control and Prevention Information System and Ningbo Regional Diagnosis and Treatment Information Platform. Factors affecting drug-induced liver injury was identified using the multivariable logistic regression analysis. **Results** A total of 9 397 patients with pulmonary tuberculosis were enrolled, among whom 66.43% (6 242 case) were male, 65.89% (6 192 cases) were at ages of <60 years, and 92.35% (8 678 cases) were treatment-naïve. There were 1 425 patients with drug-induced liver injury (15.16% incidence), including 729 cases with grade 1 (51.16%), 24 cases with grade 2 (1.68%), 7 cases with grade 3 (0.49%), 7 cases with grade 4 (0.49%), and 658 cases with ungraded drug-induced liver injury (46.18%). The median duration between drug administration and development of drug-induced liver injury was 24 (interquartile range, 44) days. Multivariable logistic regres-

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sion analysis identified treatment-naïve ($OR=1.464$, $95\%CI: 1.153-1.859$) and history of liver disease ($OR=2.001$, $95\%CI: 1.709-2.342$) as risk factors for drug-induced liver injury in patients with pulmonary tuberculosis. **Conclusion** The incidence of drug-induced liver injury was 15.16% among pulmonary tuberculosis patients in Ningbo City from 2015 to 2019. Treatment-naïve and a history of liver disease are associated with drug-induced liver injury among patients with pulmonary tuberculosis.

Keywords: pulmonary tuberculosis; drug-induced liver injury; influencing factor

药物性肝损伤是抗结核治疗过程中常见的不良反应,由抗结核药物本身和(或)其代谢产物引起,临床表现通常无特异性,潜伏期差异较大,短至1日,长达数月,多数患者无明显症状,仅有肝功能异常^[1-2]。一项多中心研究结果表明,我国药物性肝损伤发病率为23.8/10万^[3]。药物性肝损伤不仅影响患者治疗依从性,还可能导致肝衰竭危及生命。本研究收集2015—2019年宁波市肺结核患者资料,分析药物性肝损伤发生情况及其影响因素,为药物性肝损伤的早期识别和干预提供依据。

1 资料与方法

1.1 资料来源 2015—2019年宁波市肺结核患者资料来源于中国疾病预防控制中心结核病管理信息系统,由结核病定点医院接诊医生登记病案信息,经区(县)疾病预防控制中心审核后上报。肺结核患者临床诊疗、实验室检测和疾病史等资料来源于宁波市区域诊疗信息平台。纳入标准:经二级及以上结核病定点医院确诊;本次抗结核药物治疗前2周内无药物性肝损伤诊断记录;资料完整;宁波市户籍。

1.2 方法 收集2015—2019年宁波市肺结核患者的身份证号、性别、年龄、户籍、诊断日期、治疗类型、开始治疗日期和结束治疗日期等基本信息;抗结核药物治疗结束前药物性肝损伤情况(诊断日期、肝功能检验报告),抗结核药物治疗前的高血压史、糖尿病史、慢性阻塞性肺疾病史、高脂血症史、肿瘤病史、心血管疾病史、肝病史、吸烟和饮酒等诊疗信息。药物性肝损伤发生间隔时间为开始抗结核药物治疗到诊断为药物性肝损伤的天数。

1.3 定义及诊断标准 (1)2015—2016年和2017—2019年肺结核诊断分别参照WS 288—2008《肺结核诊断标准》^[4]和WS 288—2017《肺结核诊断》^[5]; (2)药物性肝损伤诊断参照《抗结核药所致药物性肝损伤诊断与处理专家建议》^[6],分级依据《抗结核药物性肝损伤诊治指南(2019年版)》^[2]:1级为血清丙氨酸氨基转移酶和(或)碱性磷酸酶可恢复性升高,总胆红素 <2.5 倍正常值上限,且凝血酶原时间

国际标准化比率 <1.5 ;2级为血清丙氨酸氨基转移酶和(或)碱性磷酸酶升高,总胆红素 ≥ 2.5 倍正常值上限,或虽无总胆红素升高但凝血酶原时间国际标准化比率 ≥ 1.5 ;3级为血清丙氨酸氨基转移酶和(或)碱性磷酸酶升高,总胆红素 ≥ 5 倍正常值上限,伴或不伴凝血酶原时间国际标准化比率 ≥ 1.5 ;4级为血清丙氨酸氨基转移酶和(或)碱性磷酸酶升高,总胆红素 ≥ 10 倍正常值上限或每日升高 $\geq 17.1 \mu\text{mol/L}$,凝血酶原时间国际标准化比率 ≥ 2.0 或凝血酶原活动度 $<40\%$,可同时出现腹水、肝性脑病或与药物性肝损伤相关的其他器官功能衰竭;5级为因药物性肝损伤死亡,或需接受肝移植才能存活;未分级为临床诊断为药物性肝损伤但没有相应血清生化结果支持。(3)初治指从未因肺结核接受过抗结核药物治疗,或抗结核药物治疗不足1个月^[7];复治指初治失败或规则用药满疗程后痰菌复阳或不规律化疗超过1个月^[8]。(4)吸烟指现在吸烟或曾经吸烟;饮酒指现在饮酒或曾经饮酒。

1.4 统计分析 采用Excel 2016软件整理数据,采用SPSS 26.0软件统计分析。定量资料不服从正态分布,采用中位数和四分位数间距 $[M(Q_R)]$ 描述,组间比较采用Kruskal-Wallis H 检验;定性资料采用相对数描述,组间比较采用 χ^2 检验。采用R 4.0.3软件Mice包多重插补法补充缺失数据。药物性肝损伤影响因素分析采用多因素logistic回归模型。检验水准 $\alpha=0.05$ 。

2 结果

2.1 药物性肝损伤发生情况 纳入肺结核患者9397例,男性6242例,占66.43%;女性3155例,占33.57%。年龄 <60 岁6192例,占65.89%。初治8678例,占92.35%;复治719例,占7.65%。发生药物性肝损伤1425例,发生率为15.16%。其中1级729例,占51.16%;2级24例,占1.68%;3级7例,占0.49%;4级7例,占0.49%;未分级658例,占46.18%。药物性肝损伤发生间隔时间的 $M(Q_R)$ 为24(44)d。不同年份药物性肝损伤发生率差异有统计学意义($P<0.05$),其中2015年发生

率较高，为 27.31%；2019 年发生率较低，为 9.20%。见表 1。

表 1 2015—2019 年宁波市肺结核患者药物性肝损伤发生情况及分级
Table 1 Incidence and severity of drug-induced liver injury in Ningbo City, 2015-2019

| 年份 Year | 例数 Cases | 发生率 Rate/% | 间隔时间 Intervals from start of treatment to onset/d [M (Q _R)] | 严重程度分级 Severity [n (%)] | | | | |
|------------------|----------|------------|--|-------------------------|-----------|----------|----------|--------------|
| | | | | 1 | 2 | 3 | 4 | 未分级 Ungraded |
| 2015 | 435 | 27.31 | 25 (41) | 224 (51.49) | 5 (1.15) | 1 (0.23) | 2 (0.46) | 203 (46.67) |
| 2016 | 308 | 16.73 | 15 (39) | 170 (55.19) | 5 (1.62) | 1 (0.32) | 1 (0.32) | 131 (42.53) |
| 2017 | 223 | 10.99 | 28 (56) | 117 (52.47) | 5 (2.24) | 3 (1.35) | 0 (0) | 98 (43.95) |
| 2018 | 288 | 13.88 | 26 (43) | 136 (47.22) | 7 (2.43) | 1 (0.35) | 1 (0.35) | 143 (49.65) |
| 2019 | 171 | 9.20 | 21 (49) | 82 (47.95) | 2 (1.17) | 1 (0.58) | 3 (1.75) | 83 (48.54) |
| 合计 Total | 1 425 | 15.16 | 24 (44) | 729 (51.16) | 24 (1.68) | 7 (0.49) | 7 (0.49) | 658 (46.18) |
| χ ² 值 | | 267.648 | 7.062 ^a | | | 17.965 | | |
| P 值 | | <0.001 | 0.133 ^a | | | 0.326 | | |

注：a 表示组间比较采用 Kruskal-Wallis H 检验。Note: a, using Kruskal-Wallis H test.

2.2 药物性肝损伤影响因素的单因素分析 以药物性肝损伤为因变量 (0=否, 1=是) 进行单因素 logistic 回归分析。结果显示, <60 岁、初治、无高血压史、无肿瘤史和有肝病史的患者药物性肝损伤发生率相对较高 (P<0.05)。见表 2。

表 2 药物性肝损伤的单因素 logistic 回归分析
Table 2 Univariable logistic regression analysis of influencing factors for drug-induced liver injury

| 变量 Variable | 调查人数 Cases with tuberculosis | 药物性肝损伤例数 Cases with drug-induced liver injury | 发生率 Rate/% | P 值 | OR 值 | 95%CI |
|--|------------------------------|---|------------|--------|-------|---------------|
| 性别 Gender | | | | | | |
| 男 Male | 6 242 | 931 | 14.92 | | 1.000 | |
| 女 Female | 3 155 | 494 | 15.66 | 0.343 | 1.059 | 0.941 ~ 1.192 |
| 年龄/岁 Age/Year | | | | | | |
| <60 | 6 192 | 994 | 16.05 | | 1.000 | |
| ≥60 | 3 205 | 431 | 13.45 | 0.001 | 0.812 | 0.719 ~ 0.918 |
| 治疗类型 Type of treatment | | | | | | |
| 复治 Treatment-experienced | 719 | 83 | 11.54 | | 1.000 | |
| 初治 Treatment-naïve | 8 678 | 1 342 | 15.46 | 0.005 | 1.402 | 1.107 ~ 1.775 |
| 高血压史 History of hypertension | | | | | | |
| 无 No | 8 372 | 1 307 | 15.61 | | 1.000 | |
| 有 Yes | 1 025 | 118 | 11.51 | <0.001 | 0.703 | 0.575 ~ 0.860 |
| 糖尿病史 History of diabetes | | | | | | |
| 无 No | 8 934 | 1 367 | 15.30 | | 1.000 | |
| 有 Yes | 463 | 58 | 12.53 | 0.105 | 0.793 | 0.598 ~ 1.050 |
| 慢性阻塞性肺疾病史 History of chronic obstructive pulmonary disease | | | | | | |
| 无 No | 9 366 | 1 424 | 15.20 | | 1.000 | |
| 有 Yes | 31 | 1 | 3.23 | 0.098 | 0.186 | 0.025 ~ 1.364 |
| 高脂血症史 History of hyperlipidemia | | | | | | |
| 无 No | 9 365 | 1 419 | 15.15 | | 1.000 | |

表 2 (续) Table 2 (continued)

| 变量 Variable | 调查人数 Cases with tuberculosis | 药物性肝损伤例数 Cases with drug- induced liver injury | 发生率 Rate/% | P 值 | OR 值 | 95%CI |
|---|------------------------------------|--|---------------|---------|-------|---------------|
| 有 Yes | 32 | 6 | 18.75 | 0.572 | 1.292 | 0.531 ~ 3.145 |
| 肿瘤史 History of tumor | | | | | | |
| 无 No | 9 322 | 1 420 | 15.23 | | 1.000 | |
| 有 Yes | 75 | 5 | 6.67 | 0.047 | 0.397 | 0.160 ~ 0.987 |
| 心血管疾病史 History of cardiovascu- lar disease | | | | | | |
| 无 No | 9 316 | 1 419 | 15.23 | | 1.000 | |
| 有 Yes | 81 | 6 | 7.41 | 0.057 | 0.445 | 0.193 ~ 1.025 |
| 肝病史 History of liver disease | | | | | | |
| 无 No | 8 393 | 1 181 | 14.07 | | 1.000 | |
| 有 Yes | 1 004 | 244 | 24.30 | < 0.001 | 1.961 | 1.676 ~ 2.293 |
| 吸烟 Smoking | | | | | | |
| 无 No | 7 554 | 1 148 | 15.20 | | 1.000 | |
| 有 Yes | 1 843 | 277 | 15.03 | 0.857 | 0.987 | 0.865 ~ 1.138 |
| 饮酒 Drinking | | | | | | |
| 无 No | 8 531 | 1 280 | 15.00 | | 1.000 | |
| 有 Yes | 866 | 145 | 16.74 | 0.174 | 1.139 | 0.944 ~ 1.375 |

2.3 药物性肝损伤影响因素的多因素 logistic 回归分析 以药物性肝损伤为因变量 (0=否, 1=是), 以年龄、治疗类型、高血压史、慢性阻塞性肺疾病史、肿瘤史、心血管疾病史和肝病史为自变量, 进行多因素

logistic 回归分析 (全入法)。结果显示, 初治和肝病史是药物性肝损伤的危险因素; 剔除严重程度为未分级的个案后结果仍显示, 初治和肝病史是药物性肝损伤的危险因素。见表 3。

表 3 药物性肝损伤影响因素的多因素 logistic 回归分析

Table 3 Multivariable logistic regression analysis of influencing factors for drug-induced liver injury

| 模型 Model | 变量 Variable | 参照组 Reference | β | $s_{\bar{x}}$ | Wald χ^2 值 | P 值 | OR 值 | 95%CI |
|--|------------------------------|--------------------------|---------|---------------|-----------------|---------|-------|-------------|
| 未剔除未分级个案 With ungraded cases (n=9 397) | 治疗类型 Type of treatment | | | | | | | |
| | 初治 Treatment-naïve | 复治 Treatment-experienced | 0.381 | 0.122 | 9.762 | 0.002 | 1.464 | 1.153~1.859 |
| | 肝病史 History of liver disease | | | | | | | |
| | 有 Yes | 无 No | 0.693 | 0.080 | 74.216 | < 0.001 | 2.001 | 1.709~2.342 |
| | 常量 Constant | | -2.093 | 0.122 | 291.842 | < 0.001 | 0.123 | |
| 剔除未分级个案 Without ungraded cases (n=8 739) | 治疗类型 Type of Treatment | | | | | | | |
| | 初治 Treatment-naïve | 复治 Treatment-experienced | 0.347 | 0.160 | 4.684 | 0.030 | 1.414 | 1.033~1.936 |
| | 肝病史 History of liver disease | | | | | | | |
| | 有 Yes | 无 No | 0.448 | 0.111 | 16.175 | < 0.001 | 1.565 | 1.258~1.947 |
| | 常量 Constant | | -2.664 | 0.161 | 274.933 | < 0.001 | 0.070 | |

3 讨论

研究结果显示,宁波市肺结核患者药物性肝损伤发生率为15.16%,与河北省保定市(16.0%)^[9]和陕西省西安市(15.3%)^[10]调查结果接近。我国肺结核治疗多采用2HRZE/4HR化疗方案:前2个月为强化期,使用异烟肼、利福平、吡嗪酰胺和乙胺丁醇4种抗结核药物进行联合治疗;后4个月为巩固期,使用异烟肼和利福平2种抗结核药物进行联合治疗^[9]。有研究表明,异烟肼、利福平和吡嗪酰胺联用引起肝损伤的风险是异烟肼和利福平联用的3倍^[11]。提示强化期是药物性肝损伤的多发时间窗口,临床治疗过程中应重视强化期肝功能监测,采取相应干预措施。本研究药显示物性肝损伤发生间隔时间中位数为24d,多数药物性肝损伤发生在治疗强化期内,与既往研究^[11]一致。

多因素logistic回归分析结果显示,与复治患者相比,初治患者更容易发生药物性肝损伤,可能与初治患者对抗结核药物不耐受、复治患者化疗方案多采用低肝脏毒性的氟喹诺酮类药物^[12]有关。肝病是药物性肝损伤的危险因素,与既往研究结果^[13]一致,可能与代谢酶活性下降、药物在肝脏内蓄积有关^[14]。

建议对初治和有肝病史的肺结核患者增加治疗强化期的随诊和肝功能检查次数。本研究利用区域诊疗信息平台与疾病监测数据库开展调查,具有研究成本低、样本代表性好和数据来源可靠等优点。尽管部分药物性肝损伤临床诊断缺乏实验室证据支持,但剔除这些病例前后得出的药物性肝损伤危险因素基本一致,结论稳定性较好。

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