Article

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Causal Association of Total Bilirubin and Albumin Levels with Lung Cancer Risk: A Mendelian Randomization Study

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Background: Our study aimed to examine the causal relationship between total bilirubin and albumin levels and the risk of developing lung cancer (LC). Previous studies have suggested that the antioxidant properties of these two biomarkers may potentially inhibit cancer development. However, the available evidence on the relationship between total bilirubin and albumin levels and the risk of LC remains inconsistent.

Method: We conducted a two-sample Mendelian randomization (TSMR) study to investigate the association between total bilirubin and albumin levels and the risk of developing LC and assess their causality. We retrieved aggregate statistical datasets from publicly accessible genome-wide association studies (GWAS) of bilirubin and albumin and utilized them as the exposure.

Results: Our findings indicated that bilirubin and albumin levels were associated with an increased risk of LC. The findings were as follows: bilirubin: odds ratio (OR) = 1.341%, 95% confidence interval (CI): 1.076–1.672, $p = 0.009$; albumin: OR = 1.582%, 95% CI: 1.077–2.323, $p = 0.019$.

Conclusion: This TSMR analysis indicates that bilirubin and albumin levels positively correlate with an increased risk of LC. These findings contribute to a deeper comprehension of the causes of LC and offer insights into its prevention.

Keywords: bilirubin; albumin; lung cancer; Mendelian randomization

Introduction

For decades, lung cancer (LC) has maintained its position as the leading cause of cancer-related fatalities across the globe. This aggressive form of cancer spreads swiftly and invades surrounding tissues, leading to over one million deaths annually [1]. Timely identification and intervention for individuals at risk or belonging to a high-risk population are crucial in reducing the LC mortality rate. This is particularly significant for individuals with pre-existing health issues that can elevate the likelihood of developing malignancies [2].

Antioxidants function as scavengers of free radicals, effectively countering the harmful effects caused by excessive reactive oxygen species [3]. Moreover, they are potentially protective agents against cancer [4]. The potent antioxidant properties of bilirubin and albumin have garnered increasing interest as potential cancer-preventing agents. Their ability to reduce inflammation and inhibit the proliferation of tumor cells has driven this interest [5]. Bilirubin and albumin possess intrinsic antioxidant properties [6]. Bilirubin demonstrates significant antioxidant effects and has been proven to alleviate age-related inflammation and metabolic decline in experimental rodent models [7]. The connection between inflammation and cancer has been recognized for a considerable time. Consequently, it has been widely speculated that natural substances capable of alleviating inflammation might potentially possess properties of cancer prevention. Furthermore, other mechanisms suggest that bilirubin plays a protective role in reducing cancer risk. Albumin exhibits multiple functions, including scavenging and antioxidant activities [8]. These functions may reflect the individual and nutritional status [9]. Despite the ability of the cell to break down albumin, it still supplies amino acids essential for cell growth and matrix formation. Reduced levels of albumin in the blood are commonly linked to significant inflammation or malnourishment [10]. However, a prospective study found no significant link between bilirubin and albumin levels and the incidence of LC [11]. A large cohort study conducted by Wen CP *et al.* [12] showed that an increase in bilirubin levels potentially reduced the risk of LC. Similarly, a cohort study conducted by Lim JE *et al.* [13] indicated that higher baseline bilirubin levels within the normal range were associated with a lower risk of LC. Conversely, a prospective cohort study by Sprague BL *et al.* [14] demonstrated no association between serum albumin and LC risk. Moreover, a meta-analysis of these studies revealed that total bilirubin levels showed inverse association with the likelihood of LC occurrence [15]. However, given the contradictory na-

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ture of these findings, it became necessary to re-identify the causal relationship of bilirubin and albumin with the progression of LC.

Mendelian randomization (MR) is grounded in the concept that an individual's genetic makeup is determined randomly during conception [16]. It employs genetic variations as instrumental variables (IVs) to establish the relationship between phenotypic exposures and outcomes, thereby eliminating bias caused by unmeasured confounding factors. For a genetic variant to be used as IV, it must satisfy the following assumptions: (1) it is linked to the exposure, (2) it impacts the outcome solely through the exposure, and (3) it is not linked to any confounding factors affecting the association between the exposure and outcome [17].

MR analysis has become a widespread approach for estimating unconfounded associations between exposure and outcome by identifying a genetic marker that meets the necessary IV assumptions [18].

In this study, we performed a two-sample Mendelian randomization (TSMR) analysis to assess the relationship between bilirubin and albumin levels and the risk of developing LC. Our analysis utilized the single nucleotide polymorphisms (SNPs) associated with bilirubin and albumin as IVs. For this analysis, we obtained the necessary aggregate statistics from recent large-scale genome-wide association studies (GWAS).

Material and Method

Data Sources and Selection of Genetic Variants

We conducted a search on the GWAS summary data available at http://gwas.mrcieu.ac.uk, which contains an extensive compilation of summary statistics from various GWAS. For this study, we used a publicly available aggregated statistical dataset relating to total bilirubin levels (n = 388,303) and albumin levels (n = 115,064) in individuals of European ancestry as our exposure variables. We utilized a TSMR analysis to investigate the impact of genetic variations linked to total bilirubin and albumin levels. This analysis served as the IV to enhance inference, using a *p*-value threshold of 5.00×10^{-8}, which is considered significant at the genome-wide level. Consequently, we retrieved 148 SNPs associated with total bilirubin and 22 SNPs associated with albumin levels from the GWAS dataset (beta coefficient and standard error). As a result, we used publicly accessible aggregate statistical datasets from GWAS conducted on 178,726 individuals, including 4444 LC cases and 74,282 controls.

Statistical Analysis of Mendelian Randomization

We employed R software (version 4.2.1, https://www.r-project.org/), the TwoSampleMR software package (version 0.5.6), and the MR-peliosis residual and outlier method (MRPRESSO) software package (version 1.0) for data analysis [19]. Genetic variations are used as instrumental variables (IVs) in MR analysis to assess the causal impact of risk factors in complex diseases [20].

The primary analysis used the inverse-variance weighted (IVW) method [21]. Additionally, various complementary MR Assays were used to accurately assess causal effects and account for the impact of horizontal pleiotropy. These techniques include the weighted median approach, weighted mode approach, simple mode approach, MR-Egger regression method, and MR-peliosis residual and outlier method (MR-PRESSO) [22,23]. To acquire IVs, we utilized the clumping technique using a linkage disequilibrium (LD) reference panel derived from the 1000 Genomes Project. Clumping was performed based on the criteria of an R^2 value below 0.001 within a 1000-kb distance [24], and IVs were obtained according to a significance threshold of $p < 5 \times 10^{-8}$. In the presence of effect allele frequency (EAF) values, we used EAF and estimated effect (BETA) to calculate the R^2 and F-statistic for evaluating the strength of IV [25]. All F-statistics exceeded 10.

The IVW is a reliable analysis based on the assumption that all genetic variants serve as valid IVW and possess a strong capability to identify causal relationships [26]. However, due to differences in experimental conditions, selected populations, and SNP, TSMR analyses may exhibit heterogeneity, potentially leading to biased estimates of causal effects. To address this issue, we propose coordinating SNPs that exclude incompatible alleles and SNPs that exclude palindromic alleles with intermediate allele frequencies. As a result, we conducted a heterogeneity test for the MR results. The *p*-value obtained from the test exceeded 0.05, indicating no evidence of heterogeneity between IVs. One fundamental assumption of the MR analysis is that IV exerts an effect on the results only through its impact on exposure. Therefore, it is crucial to assess and detect horizontal pleiotropy when examining the causal relationship between exposure and outcome [27]. The intercept term when close to zero indicates a close resemblance of the MR-Egger regression model to the IVW. The smaller the possibility of horizontal pleiotropy, the less significant the pleiotropy effect, suggesting that SNPs are only related to exposure and remain unaffected by other confounding factors [28]. Furthermore, we investigated the presence of pleiotropy using the *p*-value derived from the pleiotropy test. A *p*-value exceeding 0.05 indicates minimal or absent pleiotropy in the causal analysis, with its effect considered negligible. Additionally, to verify the study results, we conducted a leave-one analysis to evaluate the consistency of the findings [29].

Results

Causal Effects of Total Bilirubin Levels on LC

In the TSMR analysis, 148 SNPs were identified, representing the relationship between total bilirubin levels as the exposure variable and LC as the outcome variable. The

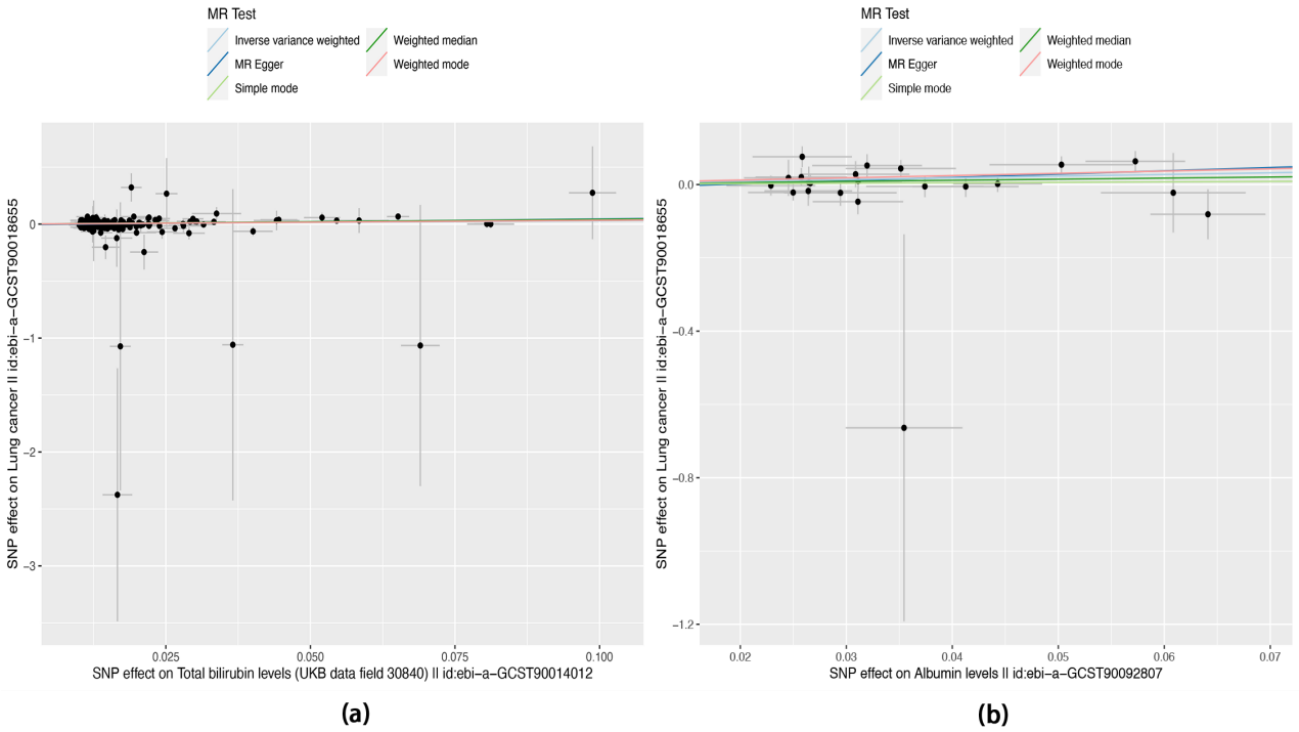

Fig. 1. The scatterplot shows a genetic association of total bilirubin and albumin levels with LC. (a) Genetic association of total bilirubin levels with LC and (b) genetic association of albumin levels with LC.

Table 1. MR estimates the relationship between total bilirubin and albumin levels with LC.

Outcome	Exposure	Method	OR	95% CI	*p*-value
LC	Total bilirubin levels	MR Egger	1.648	1.079–2.516	0.021
		Weighted median	1.517	1.073–2.146	0.018
		IVW	1.341	1.075–1.672	0.009
		Simple mode	1.393	0.712–2.728	0.334
		Weighted mode	1.393	0.899–2.159	0.139
LC	Albumin levels	MR Egger	2.454	0.618–9.743	0.216
		Weighted median	1.340	0.787–2.283	0.280
		IVW	1.581	1.077–2.323	0.019
		Simple mode	1.130	0.433–2.949	0.804
		Weighted mode	1.846	0.969–3.514	0.076

Note: MR, Mendelian randomization; LC, lung cancer; OR, odds ratio; CI, confidence interval; IVW, inverse-variance weighted.

Table 2. Heterogeneity of Wald ratios and MR-Egger test for directional pleiotropy.

Exposure	Heterogeneity				MR-Egger test for directional pleiotropy		
	Outcome	*Q*	df	*p*-value	Intercept	SE	*p*-value
Total bilirubin levels	LC	158.958	147	0.236	–0.005	0.004	0.265
Albumin levels	LC	25.926	21	0.209	–0.016	0.025	0.522

Note: *Q*, the Q statistic measures the total heterogeneity among the Wald ratios (instrumental variable estimates) of individual genetic variants; df, degrees of freedom represent the number of independent values or quantities that can be assigned to a statistical distribution; SE, standard error.

findings were as follows: IVW (odds ratio (OR) = 1.341, 95% confidence interval (CI) = 1.075–1.672, $p = 0.009$), MR-egger (OR = 1.648, 95% CI = 1.079–2.516, $p = 0.021$), and weighted median (OR = 1.517, 95% CI = 1.073–2.146, $p = 0.018$). These outcomes indicate that total bilirubin levels are risk factors for LC (Table 1 and Fig. 1a). Table 2

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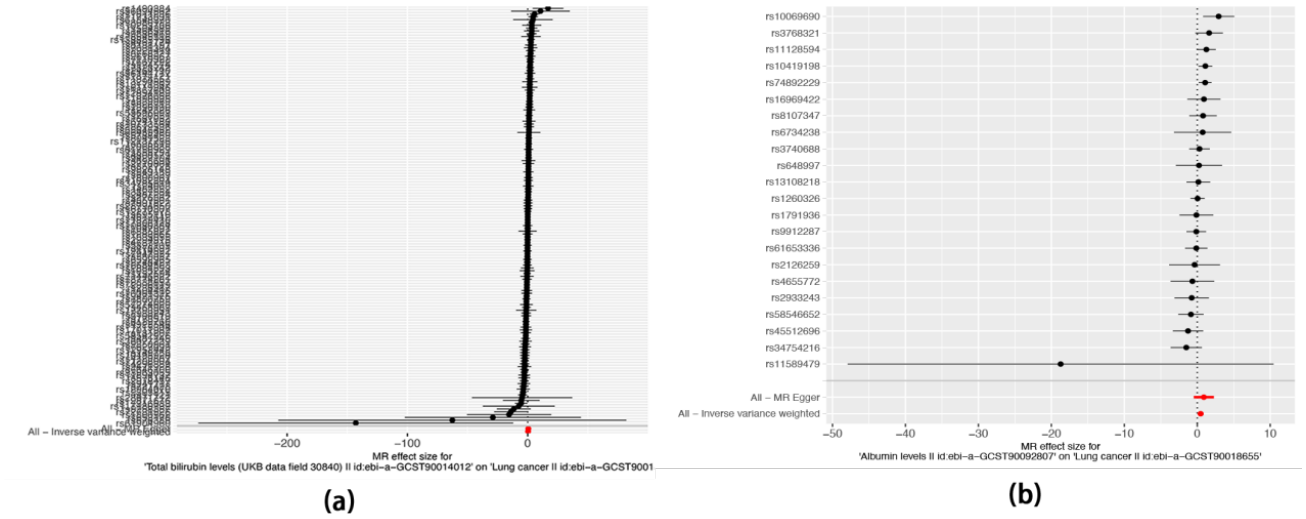

Fig. 2. Forest plots of causal effects of total bilirubin levels-associated SNPs on LC (a) and albumin levels-associated SNPs on LC (b). Note: SNPs, single nucleotide polymorphisms.

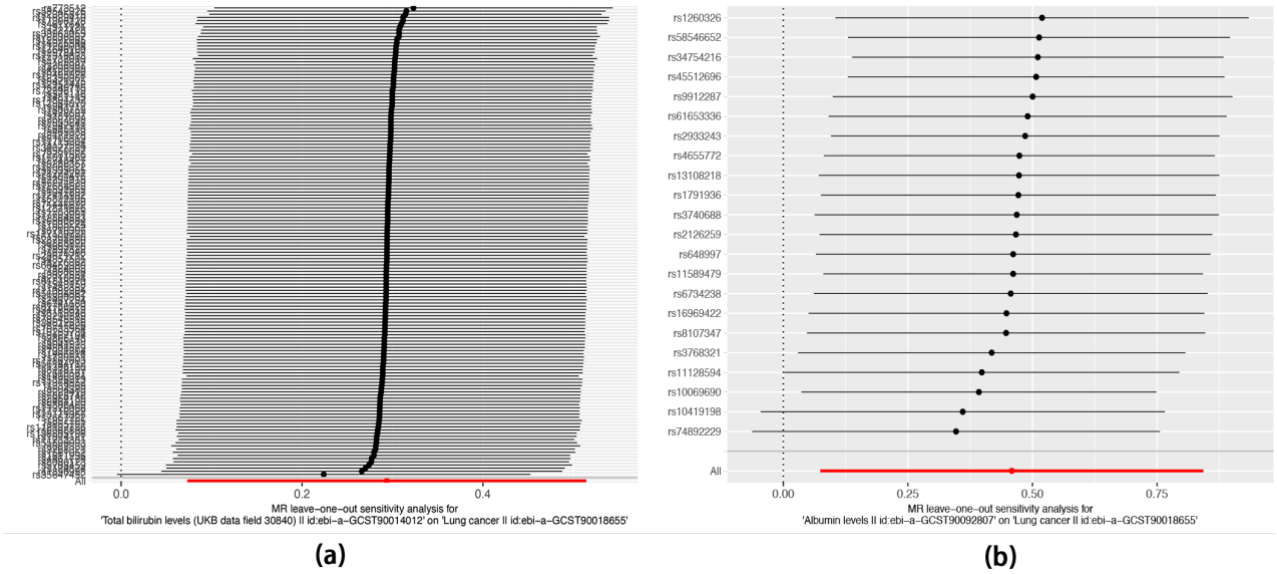

Fig. 3. Leave-one-out analysis of SNP associated with bilirubin levels and LC (a) and albumin levels and LC (b).

displays the relationship between total bilirubin levels and the risk of LC, indicating no heterogeneity among the IVs with a *p*-value of 0.236. Furthermore, the MR-PRESSO method demonstrated no potential horizontal pleiotropy between them ($p = 0.242$). The Forest plots in Fig. 2a depict the impact of SNP effect sizes on total bilirubin levels. Additionally, the leave-one-out analysis (Fig. 3a) reveals the absence of significant outliers or high-impact points. These results support a genetic relationship between total bilirubin levels and LC (Fig. 4a).

Causal Effects of Albumin Levels on LC

We investigated the relationship between albumin levels as exposure and LC as the outcome. Our findings revealed the association of 22 SNPs with these variables. Our analysis revealed significant correlations between LC and albumin levels, as shown by the IVW (OR = 1.581, 95% CI = 1.077–2.323, $p = 0.019$), MR-egger (OR = 2.454, 95% CI = 0.618–9.743, $p = 0.216$), and weighted median (OR = 1.340, 95% CI = 0.787–2.283, $p = 0.280$) methods (Table 1 and Fig. 1b). The MR-Egger analysis did not indicate the presence of horizontal pleiotropy, as evidenced by the intercept value (–0.016) and *p*-value (0.522) in Table 2 and Fig. 2b. Additionally, the MR-PRESSO method validated the absence of horizontal pleiotropy between them ($p = 0.211$). Furthermore, the leave-one-out analysis yielded no significant abnormalities, as shown in Fig. 3b. These findings confirm a genetic association between albumin levels and LC, as depicted in Fig. 4b.

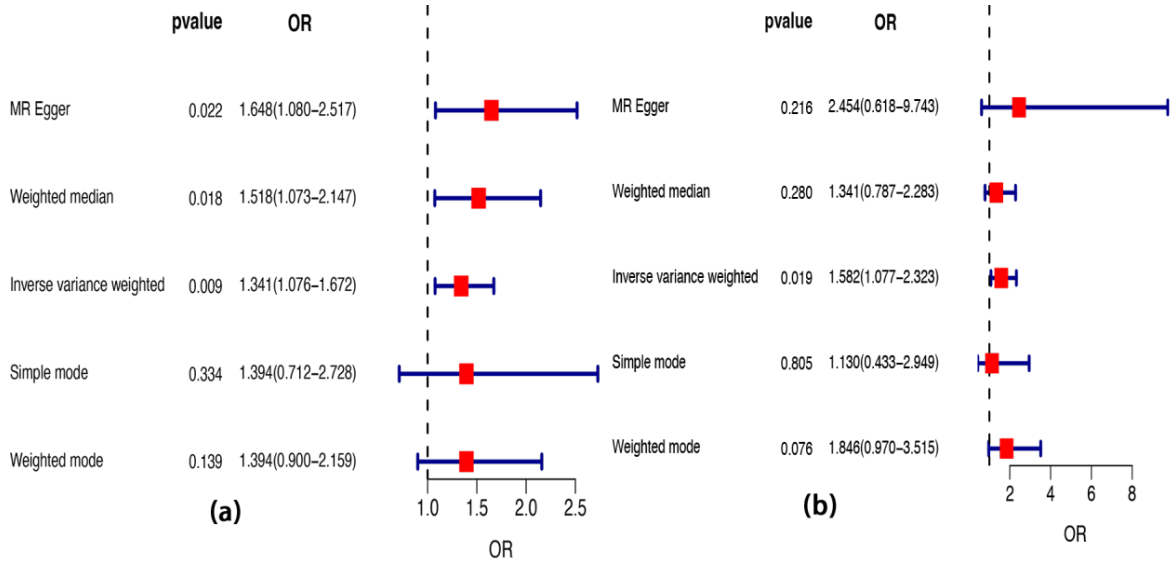

Fig. 4. Mendelian randomization estimates the relationship between bilirubin levels with LC (a) and albumin levels with LC (b).

Discussion

Horsfall *et al*. [30] conducted a large-scale Mendelian randomized study utilizing data from the UK biobank, focusing on adults. The results showed that every 5 μmol/L increase in circulating total bilirubin would reduce the overall incidence of lung cancer by 1.2/10,000 people/year. This indicates the role of bilirubin as an immuno-modulator, as evidenced by its ability to suppress CD4 T cell responses [31]. The presence of CD4-positive T cells and their associated cytokines is linked to an increased susceptibility to lung cancer [32]. Human blood albumin indicates the nutritional state of the body, and as a negative acute phase protein, it also reflects the inflammatory state. The association between serum albumin and inflammation is further supported by the inverse correlation observed between serum albumin levels and markers, including C-reactive protein and tumor necrosis factor-a [33].

Previous observational studies have reported the effects of total bilirubin and albumin levels on LC [34,35]. However, the role of total bilirubin and albumin levels in LC remains controversial. While several mouse tumor models have demonstrated the cancer-preventing abilities of antioxidants, suggesting their potential to theoretically inhibit tumorigenesis [36], our study indicates a contradictory perspective. In this TSMR study using the latest GWAS data, we found a positive causality between total bilirubin and albumin levels and the risk of LC. Research has underscored the dual nature of antioxidants, capable of both promoting and preventing cancer [37]. Antioxidants play a pivotal role in neutralizing reactive oxygen species (ROS), thereby protecting the cellular macromolecules of healthy cells against ROS-induced damage. However, this beneficial function of antioxidants can also assist cancer cells [38]. Cancer cells exhibit elevated levels of reactive oxygen species (ROS) compared to normal cells. To counteract this heightened ROS level, cancer cells develop a stronger antioxidant defense system. Consequently, excessive ROS production can contribute to carcinogenesis. However, the presence of both endogenous and exogenous antioxidants can scavenge these ROS, potentially promoting cancer development. This theory is consistent with the findings from our MR results.

There are several limitations to be considered in this MR study. Firstly, the analysis is constrained by the statistical limitation in MR analysis of genetic aggregation, which may restrict the scope of our analysis. Additionally, it is essential to acknowledge that individual differences among participants can also impact the findings. However, due to the utilization of multiple supplementary methods, the effect estimates all exceed 1, indicating a low likelihood of biased results. MR analysis typically offers compelling evidence, particularly when the effect size is minimal or absent [39]. Currently, most clinical studies rely on blood samples collected after diagnosis to explore the characteristics of circulatory metabolomics. However, these data may be biased by various factors, including chemotherapy, surgery, lifestyle, and other factors, without appropriate control over these factors. Therefore, it is necessary to reasonably divide and further elucidate these factors to assess the relationship between bilirubin and albumin levels and the occurrence and development of LC.

Conclusion

In summary, this TSMR analysis indicates that bilirubin and albumin levels positively correlate with an increased LC risk. These findings contribute to a deeper comprehension of the causes of LC and offer insights into its prevention.

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Availability of Data and Materials

The corresponding author can provide the datasets generated and analyzed during the current study upon reasonable request.

Author Contributions

QL designed the research study. QL performed the research. QL analyzed the data. QL drafted this manuscript. The author contributed to the editing of the manuscript. The author read and approved the final manuscript. The author agreed to take responsibility for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

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Conflict of Interest

The author declares no conflict of interest.

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