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Original Research

Levels of serum bilirubin in small cell lung cancer and non-small cell lung cancer patients

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Abstract: Elevated bilirubin has been associated with protection of cardiovascular and kidney systems, whereas decreased bilirubin may predispose respiratory diseases. However, whether serum bilirubin levels are associated with lung cancer remains unclear. Here, clinical and pathologic data of a cohort of 363 lung cancer patients along with 363 age-and gender-matched healthy subjects were collected. The association of serum bilirubin levels with lung cancer was analyzed. The levels of serum bilirubin were significantly lower in lung cancer patients. The aspartate transaminase and alkaline phosphatase levels were significantly higher in lung cancer. Multi-classification logistics regression analysis revealed low total bilirubin level [OR (95%CI), 1.12 (1.02-1.23)], aspartate transaminase [OR (95%CI), 1.12 (1.02-1.23)], and alanine transaminase [OR (95%CI), 1.12 (1.02-1.23)] were risk factors in lung cancer. Serum bilirubin levels were significantly changed among small cell lung cancer (SCLC), lung adenocarcinoma (LAC) and lung squamous cell carcinoma (LSC). Total bilirubin level, smoke history and heart disease were risk factors for subtypes. Compared with LSC, patients with smoke history had significant higher risk in LAC [OR (95% Confidence Interval, CI), 4.49 (1.70, 11.96)]. Compared with LSC, patients with smoke history [OR (95%CI), 4.49 (1.70, 11.96)] and heart disease [OR (95%CI), 4.49 (1.70, 11.96)] had significant higher risk in SCLC. Compared with SCLC, patients with low total bilirubin [OR (95%CI), 1.12 (1.02-1.23)] and heart disease [OR (95%CI), 3.52 (1.01-12.23)] had significant higher risk in LAC. Taken together, these results suggested low serum bilirubin levels are tightly associated with lung cancer, especially with LAC. Serum bilirubin levels might serve as a predictor for lung cancer patients clinically.

Key words: Bilirubin; Small cell lung cancer; Non-small lung cancer; Lung adenocarcinoma; Lung squamous cell carcinoma.

Introduction

Lung cancer is one of the most common cancers leading to cancer-related death worldwide (1). In US, 224,210 new cases of lung cancer are estimated for the year 2014 with 159,260 estimated deaths (2). Based on the morphology of lung cancer cells, lung cancers are categorized into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) (3). Surgery, radio- and chemo-therapies are involved in lung cancer treatments (4, 5). Specifically, NSCLC includes lung adenocarcinoma (LAC) and lung squamous cell carcinoma (LSC), which is usually treated with surgery, while SCLC commonly gives better responses to chemotherapy and radiotherapy (3, 6). Of all patients diagnosed with lung cancer in US, only 16.8% could survive for five years, which is mainly due to the fact that the lung cancer stage is already advanced upon diagnosis (7). Currently, available diagnosis methods for lung cancer include chest radiographs, computed tomography (CT) scans and biopsy (5). In this scenario, to achieve better prognosis outcomes, identification of early lung cancer biomarkers or development of new diagnosis techniques that could detect lung cancer at earlier stage would be promising research directions (4, 8).

Bilirubin is an orange yellow pigment belonging to the superfamily of tetrapyrrolic compounds, and is the end break-down products of hemoglobin from recycled red blood cells (9, 10). For a long time bilirubin was considered as a toxic waste metabolite, however, more and more clinical and experimental evidences suggest that physiologically it plays critical roles in human body mainly serving as a cellular antioxidant (11, 12). For example, elevated levels of bilirubin prevents cardiovascular disease as well as other metabolic syndromes (13). Furthermore, negative correlations were observed between bilirubin levels and coronary artery disease, stroke, non-alcoholic fatty liver metabolic syndrome, chronic kidney diseases and some respiratory diseases (14, 15).

In most primary care center, the level of total serum bilirubin is measured as a routine index for liver diseases (10, 16). Normal ranges for bilirubin in clinical lab are from 0.1 to 1 mg/dL of total serum bilirubin (10). The total serum bilirubin levels could be affected by many factors, including genetic variations such as UGT1A1 (15), smoking, gender, fasting, drugs used, and age (17). Clinically, elevated total serum bilirubin levels may indicate liver damage or diseases, while low levels of serum bilirubin began to be linked to incidence with various cancers including kidney disorders (14) and chronic obstructive pulmonary diseases (15). The animal model studies suggested a beneficial effect of elevated bilirubin levels in protecting respiratory injury

upon environmental stress (18), while corresponding studies in human subjects are underdeveloped.

Here, we examined the association of serum levels of bilirubin and the incidence of lung cancer in a cohort of primary care lung cancer patients in China.

Materials and Methods

Patients and samples

We used information from a cohort study of primary care data recorded between January 1st, 2015, and December 31st, 2016 in Shijiazhuang, China. A total of 363 lung cancer patients (58.7±9.8 year; 111/252 female/male), along with 363 age and gender matched healthy subjects (59.6±10.6 year; 124/239 female/male) were enrolled. The study was approved by ethical committee of Forth Hospital of Hebei Medical University and informed consent was signed by each subject.

All data on diagnose records, symptoms, referrals and prescriptions were recorded electronically and maintained by healthcare professionals. Information on variables such as gender, age, height, weight, subtypes of lung cancer, and history (smoke, heart disease, hypertension, diabetes, cerebrovascular disease, pulmonary benign disease) were recorded. Fasting venous blood collected was collected from hospitalized patients and separated into fresh non-hemolytic serum and plasma by centrifugation in the presence of heparin (0.1 mg heparin anticoagulation/1.0 mL blood) and EDTA anticoagulant (1.8 mg EDTA/1.0 mL blood). Measurements including aspartate transaminase (AST), Alanine transaminase (ALT), total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, r-glutamyl transglutaminase were performed.

Measurements

Measurements including aspartate transaminase (AST), Alanine transaminase (ALT), total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, and r-glutamyl transglutaminase were determined by the vanadate oxidation methods with the commercial kit (Biological Technology Co., Ltd., Sichuan Mike, China) on BECKMAN COULTER AU5800 and BECKMAN COULTER UniCel DxC 800 Synchron Clinical System.

Statistics analysis

Data was present as mean± standard deviation (SD). One-way analysis of variance (ANOVA) was used for continuous variables. Classification variables was analyzed using chi-square test (X^2). Risk factors were analyzed by multi-classification logistics regression. All tests were detected with significance statistical level at 0.05.

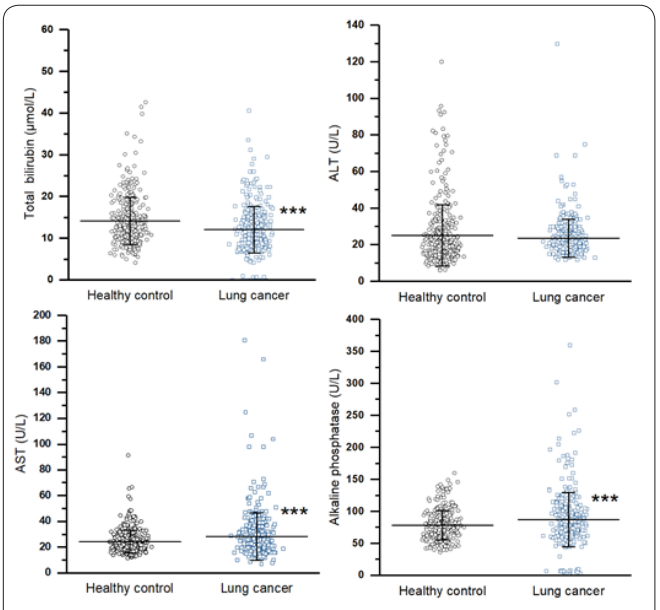

Figure 1. Levels of total bilirubin, ALT, AST, and alkaline phosphatase in 363 lung cancer patients and 363 healthy subjects. ***P<0.001.

Results

Total bilirubin levels are lower in lung cancer patients than healthy subjects

The total of 363 adult patients with lung cancer and 363 age- and gender-matched healthy subjects were recruited in this study. Levels of total bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase were analyzed (Figure 1). Results showed that the levels of serum bilirubin were significantly lower in lung cancer patients compared with healthy subject control group. AST and alkaline phosphatase levels were significantly higher in lung cancer. It was suggested that low serum bilirubin levels, high AST and alkaline phosphatase levels are tightly associated with lung cancer in this study cohort.

Multi-classification logistics regression analysis revealed low total bilirubin level [OR (95%CI), 1.12 (1.02-1.23)], AST [OR (95%CI), 1.12 (1.02-1.23)], and ALT [OR (95%CI), 1.12 (1.02-1.23)] were risk factors in lung cancer (Table 1).

Analysis of risk factors in lung cancer subtypes

General data including gender, age, height, weight, smoke history, heart disease, hypertension, diabetes, cerebrovascular disease, pulmonary benign disease, and measurements including AST, ALT, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, and r-glutamyl transglutaminase in subtypes of lung

Table 1. Multi-classification logistics regression of risk factors (Lung cancer vs. Control).

Group	B	Std. Error	Wald	*P*	OR (95% CI)
Intercept	-.398	.305	1.708	.191	-
Total bilirubin (μmol/L)	-.070	.015	20.211	.000	0.93 (0.91-0.96)
AST (U/L)	.024	.007	11.626	.001	1.02(1.01-1.04)
Alkaline phosphatase (U/L)	.007	.003	8.153	.004	1.00 (1.00-1.01)

Table 2. ANOVA analysis of factors in small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC).

Items	LSC	LAC	SCLC	F/X^2	*P*
Sex (Female/Male, n**)**	**6/48**	**53/67[a]**	**52/137[bc]**	**20.91**	**0.00**
Age (year)	60.83±7.56	58.59±9.63	58.24±10.48	1.49	0.23
Height (cm)	167.15±6.83	165.47±7.95	167.37±6.95	2.42	0.09
Weight (kg)	67.18±8.45	64.92±14.38	67.92±9.78	2.34	0.10
Smoke (No/Yes**)**	**12/42**	**70/49[a]**	**81/105[bc]**	20.61	**0.00**
Heart disease (No/Yes**)**	**48/6**	111/8	**183/5[c]**	6.77	**0.03**
Hypertension (No/Yes)	40/14	97/22	141/45	1.76	0.41
Diabetes (No/Yes)	49/5	114/6	185/4	5.75	0.06
Cerebrovascular disease (No/Yes)	50/4	113/6	182/7	1.34	0.51
Pulmonary benign disease (No/Yes**)**	**47/7**	**115/4[a]**	**180/8 [c]**	7.67	**0.02**
Aspartate transaminase (AST, U/L)	25.54±15.55	**25.27±11.18**	**31.01±22.13[b]**	4.35	**0.01**
Alanine transaminase (ALT, U/L)	**21.07±7.20**	22.32±6.45	**25.31±12.61[c]**	5.20	**0.01**
Total bilirubin (μmol/L)	**12.39±5.18[a]**	**9.98±5.31**	**13.19±5.54[b]**	12.52	**0.00**
Direct bilirubin (μmol/L)	**5.46±2.28[a]**	**4.40±2.82**	**5.94±2.55[b]**	12.94	**0.00**
Indirect bilirubin (μmol/L)	6.95±3.25	**5.88±3.45**	**7.25±3.40[b]**	5.76	**0.03**
Alkaline phosphatase (U/L)	85.90±21.65	89.32±63.31	86.53±32.81	0.16	0.85
r-glutamyl transglutaminase (U/L)	32.98±20.42	44.76±32.69	46.93±54.20	1.80	0.17

Notes: NSCLC includes lung adenocarcinoma (LAC) and lung squamous cell carcinoma (LSC); a. LSC vs. LAC; b. LAC vs. SCLC; c. LSC vs. SCLC.

cancer were analyzed (Table 2). As an end heme metabolism product, bilirubin exists in both unconjugated/indirect and conjugated/direct states. Among small cell lung cancer (SCLC), lung adenocarcinoma (LAC) and lung squamous cell carcinoma (LSC), gender, smoke history, heart disease, pulmonary benign disease, AST level, ALT level, total bilirubin level, direct bilirubin level, and indirect bilirubin level were significant different.

Compare with LSC, there were obviously more women, smoke history, pulmonary benign disease in LAC. No significant in AST level, ALT level, total bilirubin level, direct bilirubin level, and indirect bilirubin level were observed.

Compared with LSC and LAC, there were more male patients, smoke history in SCLC. Heart disease, pulmonary benign disease, and ALT were significant higher in SCLC than LSC. AST, total bilirubin level, direct bilirubin level, and indirect bilirubin level were significant higher in SCLC than LAC.

Multi-classification logistics regression of risk factors in lung cancer subtypes

Multi-classification logistics regression analysis revealed total bilirubin level, smoke history and heart disease were risk factors for subtypes (Tables 3-5). Compared with LSC, patients with smoke history had significant higher risk in LAC [OR (95% Confidence Interval, CI), 4.49 (1.70, 11.96)] (Table 3). Compared with LSC, patients with smoke history [OR (95%CI), 4.49 (1.70, 11.96)] and heart disease [OR (95%CI), 4.49 (1.70, 11.96)] had significant higher risk in SCLC (Table 4). Compared with SCLC, patients with low total bilirubin [OR (95%CI), 1.12 (1.02-1.23)] and heart disease [OR (95%CI), 3.52 (1.01-12.23)] had significant higher risk in LAC (Table 5).

Discussion

A complete set of data was collected from a cohort of 363 lung cancer patients and another 363 matched healthy subjects in China. Bilirubin is a downstream product of heme metabolism in the human body. Its existence form in serum includes conjuncted/direct bilirubin and unconjuncted/indirect bilirubin (10). Unconjugated bilirubin is bound to albumin in plasma, which is not soluble in water. In hepatocytes, bilirubin is further conjugated with glucuronic acid and is soluble in plasma and

Table 3. Multi-classification logistics regression of risk factors (LAC vs. LSC).

Group	B	Std. Error	Wald	*P*	OR (95% CI)
Intercept	-0.85	1.10	0.59	0.44	-
AST (U/L)	-0.01	0.02	0.11	0.74	0.99 (0.95-1.04)
ALT (U/L)	0.04	0.04	1.26	0.26	1.04 (0.97-1.13)
Total bilirubin (μmol/L)	-0.11	0.08	1.86	0.17	0.89 (0.76-1.05)
Direct bilirubin (μmol/L)	-0.03	0.13	0.06	0.81	0.97 (0.75-1.25)
Indirect bilirubin (μmol/L)	0.01	0.11	0.02	0.90	1.01 (0.82-1.26)
Sex	0.73	0.59	1.53	0.22	2.06 (0.66-6.50)
Smoke	**1.50**	**0.50**	**9.20**	**0.00**	**4.49 (1.70-11.86)**
Heart disease	0.32	0.64	0.25	0.62	1.37 (0.40-4.77)
Pulmonary benign disease	1.26	0.70	3.26	0.07	3.54 (0.90-13.95)

Table 4. Multi-classification logistics regression of risk factors (SCLC vs. LSC).

Group	B	Std. Error	Wald	*P*	OR(95% CI)
Intercept	-3.11	1.08	8.27	0.00	-
AST (U/L)	0.01	0.02	0.18	0.67	1.01 (0.97-1.05)
ALT (U/L)	0.06	0.04	2.47	0.12	1.06 (0.99-1.13)
Total bilirubin (μmol/L)	0.00	0.09	0.00	0.99	1.00 (0.85-1.18)
Direct bilirubin (μmol/L)	0.03	0.13	0.06	0.80	1.03 (0.81-1.32)
Indirect bilirubin (μmol/L)	0.00	0.11	0.00	0.98	1.00 (0.81-1.23)
Sex	0.35	0.57	0.39	0.53	1.42 (0.47-4.34)
Smoke	**0.95**	**0.47**	**4.20**	**0.04**	**2.60 (1.04-6.46)**
Heart disease	**1.57**	**0.69**	**5.25**	**0.02**	**4.83 (1.26-18.56)**
Pulmonary benign disease	1.00	0.60	2.83	0.09	2.73 (0.85-8.76)

Table 5. Multi-classification logistics regression of risk factors (SCLC vs. LAC).

Group	B	Std. Error	Wald	*P*	OR(95% CI)
Intercept	-2.26	1.00	5.12	0.02	-
AST (U/L)	0.02	0.01	1.39	0.24	1.02 (0.99-1.04)
ALT (U/L)	0.01	0.02	0.29	0.59	1.01 (0.97-1.06)
Total bilirubin (μmol/L)	**0.11**	**0.05**	**5.56**	**0.02**	**1.12 (1.02-1.23)**
Direct bilirubin (μmol/L)	0.06	0.09	0.55	0.46	1.07 (0.90-1.26)
Indirect bilirubin (μmol/L)	-0.02	0.06	0.07	0.79	0.98 (0.87-1.11)
Sex	-0.37	0.33	1.30	0.25	0.69 (0.36-1.31)
Smoke	-0.55	0.31	3.08	0.08	0.58 (0.31-1.07)
Heart disease	**1.26**	**0.64**	**3.91**	**0.05**	**3.52 (1.01-12.23)**
Pulmonary benign disease	-0.26	0.67	0.15	0.70	0.77 (0.21-2.84)

considered as the active form (19). In this study, overall a significant lower level of serum bilirubin was detected in lung cancer patients, regardless of age and gender, suggesting that serum bilirubin levels may be able to serve as clinical predictor for lung cancer. However, the detailed molecular mechanism behind this observation needs to be elucidated using the techniques of cell biology, biophysics and mechanobiology (20). We only tested the total bilirubin level of healthy subjects. Thus, the differences in other factors between control and lung cancer patients were not compared.

Traditionally, bilirubin is considered to be Harmful. In clinical, the level of serum bilirubin is used as a diagnostic indicator of digestive diseases and hematological diseases (21-24). Bilirubin has different effects on human body according to its level. Excessive or too low levels of bilirubin can have adverse effects on the body (25, 26). When the level of bilirubin is within the physiological range of the human body (0.8 mg/dl ~ 1.47 mg/dl), the higher the level, the stronger the protection of the body. For example, a cohort study of 500,000 people in the United Kingdom found that higher levels of bilirubin are beneficial to reduce the risk of respiratory diseases and deaths due to various causes (26). Investigations of normal blood pressure population in Korea also found bilirubin levels in normal physiology ranges were inversely associated with the incidence of hypertension, whereas higher bilirubin levels were associated with a lower incidence of hypertension (15). When angiography was performed on men without coronary heart disease, severe changes in coronary artery were found in patients with low total bilirubin levels, but the incidence of coronary heart disease was reduced by 40% to 50% in men with serum total bilirubin levels higher than 8 mg/L (0.8 mg/dl, 17 μmol/L=1 mg/dl), indicating that the high level of serum total bilirubin levels is a protective factor for coronary heart disease, and low total bilirubin level is an independent risk factor besides smoking and hypertension (27). However, serum bilirubin levels are not as high as possible. When the bilirubin level exceeds the normal physiological range, it will produce jaundice, suggesting that the lesions of body such as lesions in liver, gallbladder, pancreas and blood system might occur with a lot of adverse effects on the body. SCLC is the type with the lowest differentiation and highest malignancy in lung cancer, with rapid growth, early and widespread metastasis (28, 29). Among SCLC, LAC and LSC, gender, smoke history, heart disease, pulmonary benign disease, AST level, ALT level, total bilirubin level, direct bilirubin level, and indirect bilirubin level were significant different. No significant in AST level, ALT level, total bilirubin level, direct bilirubin level, and indirect bilirubin level were observed between LSC and LAC. AST, total bilirubin level, direct bilirubin level, and indirect bilirubin level were significant higher in SCLC than LAC. It was suggested that low bilirubin levels were high risk factors for LSC and SCLC. We acknowledge that these observations are correlations and whether there is a causal relationship between low levels of bilirubin and lung cancer require more detailed mechanistic studies in the research labs for confirmation and clarification.

Importantly, smoking is the major cause of lung cancer in both developed and developing counties, which accounts for about 85% of the cancer incidence []. Multi-classification logistics regression analysis revealed total bilirubin level, smoke history and heart disease were risk factors in lung cancer. Thus, it will

be critical to examine the relationship between serum bilirubin levels and smoking in lung cancer. However, in our study, we didn't collect enough data regarding the smoking status and leave this important question unaddressed, which warrants further investigation.

These risk factors were different in various subtype of cancers. Compared with LSC, patients with smoke history had significant higher risk in LAC [OR (95% Confidence Interval, CI), 4.49 (1.70, 11.96)]. Compared with LSC, patients with smoke history [OR (95%CI), 4.49 (1.70, 11.96)] and heart disease [OR (95%CI), 4.49 (1.70, 11.96)] had significant higher risk in SCLC. Compared with SCLC, patients with low total bilirubin [OR (95%CI), 1.12 (1.02-1.23)] and heart disease [OR (95%CI), 3.52 (1.01-12.23)] had significant higher risk in LAC.

As serum bilirubin levels are affected by many factors such as age, our study employed mainly elderly peoples and this may only reflect the correlation between serum bilirubin levels and lung cancer in a certain lung cancer patient population. Ideally larger cohort study involving lung cancer patients covering broader age may benefit the accurate analysis of the association between serum bilirubin and lung cancer incidence. This concept also applies to the fact that more men than women subjects involved in our cohort study, as it is also well-characterized that serum bilirubin levels are higher in men than in women (30).

During bilirubin generation and metabolism, several key enzymes are promising drug targets in modulating bilirubin levels. To this end, more and more experimental and clinical evidence suggest that there are therapeutic potentials for enzymes including HMOX1, BLVRA and UGT1A1, by modulating which increased serum bilirubin levels may suppress pathways leading to the development of lung cancers. Obviously, detailed understanding the pathology and molecular mechanisms underlying the regulatory axis of bilirubin, but also the whole heme catabolic pathway are likely beneficial for patients with lung cancer or other similar metabolic diseases.

Conflict of interest

None declared.

References

1. Yarmus L, Nguyen PT, Montemayor K et al. Year in review 2017: Interventional pulmonology, lung cancer, pleural disease and respiratory infections. Respirology (Carlton, Vic) Apr 11 2018.
2. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA: a cancer journal for clinicians Jan 2017; 67(1): 7-30.
3. Shroff GS, Viswanathan C, Carter BW, Benveniste MF, Truong MT, Sabloff BS. Staging Lung Cancer: Metastasis. Radiologic clinics of North America May 2018; 56(3): 411-418.
4. Shroff GS, de Groot PM, Papadimitrakopoulou VA, Truong MT, Carter BW. Targeted Therapy and Immunotherapy in the Treatment of Non-Small Cell Lung Cancer. Radiologic clinics of North America May 2018; 56(3): 485-495.
5. Ciliberto M, Kishida Y, Seki S, Yoshikawa T, Ohno Y. Update of MR Imaging for Evaluation of Lung Cancer. Radiologic clinics of North America May 2018; 56(3): 437-469.
6. Benveniste MF, Welsh J, Viswanathan C et al. Lung Cancer: Posttreatment Imaging: Radiation Therapy and Imaging Findings. Radiologic clinics of North America May 2018; 56(3): 471-483.
7. Ridge CA, McErlean AM, Ginsberg MS. Epidemiology of lung cancer. Seminars in interventional radiology Jun 2013; 30(2): 93-98.
8. Chen X, Mao G, Chen H et al. TW37 enhances the pro-apoptosis and anti-migration ability of gefitinib in Non-Small Cell Lung Cancer. Cellular and molecular biology (Noisy-le-Grand, France) Mar 31 2018; 64(4): 6-10.
9. Ramakrishnan N, Jialal I. Bilirubin, Impaired Conjugation. StatPearls. Treasure Island (FL): StatPearls Publishing; 2018.
10. Kalakonda A, John S. Physiology, Bilirubin. StatPearls. Treasure Island (FL): StatPearls Publishing; 2018.
11. Holbrook I, Beetham R, Cruickshank A et al. National audit of cerebrospinal fluid testing. Annals of clinical biochemistry Sep 2007; 44(Pt 5): 443-448.
12. Beetham R, Egner W, Patel D. The UKNEQAS scheme for cerebrospinal fluid haem pigments: a paradigm for service improvement. Annals of clinical biochemistry Nov 2011; 48(Pt 6): 489-497.
13. Vitek L. The role of bilirubin in diabetes, metabolic syndrome, and cardiovascular diseases. Frontiers in pharmacology 2012; 3: 55.
14. Ryu S, Chang Y, Zhang Y et al. Higher serum direct bilirubin levels were associated with a lower risk of incident chronic kidney disease in middle aged Korean men. PloS one 2014; 9(2): e75178.
15. Horsfall LJ, Rait G, Walters K et al. Serum bilirubin and risk of respiratory disease and death. Jama 2011; 305(7): 691.
16. Hamoud AR, Weaver L, Stec DE, Hinds TD, Jr. Bilirubin in the Liver-Gut Signaling Axis. Trends in endocrinology and metabolism: TEM Mar 2018; 29(3): 140-150.
17. Vitek L, Schwertner HA. The heme catabolic pathway and its protective effects on oxidative stress-mediated diseases. Advances in clinical chemistry 2007; 43: 1-57.
18. Ryter SW, Morse D, Choi AM. Carbon monoxide and bilirubin: potential therapies for pulmonary/vascular injury and disease. American journal of respiratory cell and molecular biology Feb 2007; 36(2): 175-182.
19. Nakagami T, Toyomura K, Kinoshita T, Morisawa S. A beneficial role of bile pigments as an endogenous tissue protector: anticomplement effects of biliverdin and conjugated bilirubin. Biochimica et biophysica acta Oct 3 1993; 1158(2): 189-193.
20. Zeng Y. Cell biology, biophysics, and mechanobiology: From the basics to Clinics. Cell Mol Biol (Noisy-le-grand) Apr 29 2017; 63(4): 1-2.
21. Zhang H, Li G, Zhu Z et al. Serum bilirubin level predicts postoperative overall survival in oral squamous cell carcinoma. Journal of oral pathology & medicine : official publication of the International Association of Oral Pathologists and the American Academy of Oral Pathology Feb 11 2018.
22. Li XH, Lin HY, Guan LY et al. Direct Bilirubin Levels and Risk of Metabolic Syndrome in Healthy Chinese Men. Biomed Res Int 2017; 2017: 9621615.
23. Li WC, Mo LJ, Shi X et al. Antioxidant status of serum bilirubin, uric acid and albumin in pemphigus vulgaris. Clinical and experimental dermatology Mar 2018; 43(2): 158-163.
24. Chen J, Wang J, Zhang X, Zhu H. Inverse Relationship Between Serum Bilirubin Levels and Diabetic Foot in Chinese Patients with Type 2 Diabetes Mellitus. Medical science monitor : international medical journal of experimental and clinical research Dec 14 2017; 23: 5916-5923.
25. Jin J, Wang W, Gu T et al. Low serum bilirubin levels contribute to the presence and progression of distal symmetrical polyneuropathy in Chinese patients with type 2 diabetes. Diabetes & metabolism Feb 22 2018.
26. Bissell MG. Serum Bilirubin and Risk of Respiratory Disease and Death. Yearbook of Pathology & Laboratory Medicine 2012;

2012: 283-284.
27. Endler G, Hamwi A, Sunderplassmann R et al. Is low serum bilirubin an independent risk factor for coronary artery disease in men but not in women? Clinical Chemistry 2003; 49(7): 1201-1204.
28. Kim DW, Kim KC, Kim KB, Dunn CT, Park KS. Transcriptional deregulation underlying the pathogenesis of small cell lung cancer. Translational lung cancer research Feb 2018; 7(1): 4-20.
29. Basumallik N, Agarwal M. Cancer, Lung, Small Cell (Oat Cell). StatPearls. Treasure Island (FL): StatPearls Publishing; 2018.
30. Rosenthal P, Pincus M, Fink D. Sex- and age-related differences in bilirubin concentrations in serum. Clinical chemistry Aug 1984; 30(8): 1380-1382.