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Subjective Global Assessment, Symptoms, Blood Nutritional Indicators and The Associated Factors in Pancreaticobiliary Tumor Patients

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ABSTRACT

Background: We aimed to investigate the subjective global assessment (SGA), symptoms and blood nutritional indicators in pancreaticobiliary tumor patients and the associated factors.

Methods: 153 pancreaticobiliary tumor patients'information was collected on admission including SGA, symptoms, blood lymphocyte count (Lmy), hemoglobin (Hb), creatinine (Cr), total cholesterol (TC), total triacylglycerol (TG), serum C-reactive protein (CRP), globulin, albumin (Alb), prealbumin (PA), transferrin (Tf), retinol binding protein (RBP) and micro-nutrients (folic acid, vit B12, vit A, vit E, vit K, vit D, iron, zinc and copper). Associated factors were explored.

Results: Advanced tumor stage, elevated CRP and CA 19-9 were risk factors for malnutrition by SGA; elevated CRP contributed to fatigue, anorexia and pain; Alb, PA and Tf decreased with age; advanced tumor stage was associated with elevated vit B12;elevated CRP was associated with decreased Hb, Alb, PA, Tf, RBP, vit A, vit D and increased globulin and copper; SGA was associated with decreased Lym, HB, Alb, PA and Tf; elevated bilirubin was associated with decreased Cr , Alb, vit K and vit D, and increased TC, TG, vit B12 and copper.

Conclusion: Inflammation should be controlled to relieve the discomforts; old patients should give more protein; advanced cancer underestimates vitB12 deficiency. Inflammation overestimates the deficiency of serum protein, vit A, vit D, iron and zinc. Malnutrition by SGA increases the deficiency of Lym and serum protein. Obstructive jaundice increases the deficiency of Cr, Alb, vit D and vitK, and cause vitB12 elevation, hyperlipemia, and copper accumulation.

INTRODUCTION

Malnutrition rate is high in pancreaticobiliary cancer Gilliland et al. (2017), Jin et al. (2021), Bye et al. (2013). Nutritional support is important for improving quality of life and prognosis. Subjective Global Assessment (SGA) and patient-generated SGA were used to identify malnourished patients who need nutritional support Detsky et al. (1987), Bauer et al. (2002). However, it is not designed to detect derangement of visceral protein and micro-nutrient. Blood nutritional indicators such as blood lymphocyte count (Lmy), hemoglobin (Hb), creatinine (Cr), triacylglycerol (TG), total cholesterol (TC), globulin, albumin (Alb), prealbumin (PA), transferrin (Tf), retinol binding protein (RBP), and serum micro-nutrient (folic acid, vitB12, vit A, vit E, vit K, vit D, iron, zinc, copper) are available in our hospital Clinical Laboratory. They can give clues of the derangement of energy, protein and micro-nutrient balance, and are helpful for better assessment and strategy making. Anemia indicates the deficiency of protein, folic acid, iron, vitB12, etc Wirth et al. (2018). Low Hb, Cr, Alb, PA, Tf and RBP might indicate caloric-protein deficiency. Creatinine is also a marker of poor muscle mass Neves et al. (2021). Low level of globulin and Lmy reflect a hypo-immunity state results from malnutrition Zhang et al. (2022). Low level of TG and TC indicate the energy deficiency Nakamura et al. (2000). Serum micro-nutrient concentration indicate the deficiency or excess of the body store. However, besides nutritional factor, other factors may affect these blood nutritional indicators such as inflammation, biliary obstruction, age, and cancer. These factors are needed to be explored to aid in the interpretation of results and accurate nutritional assessment to guide the nutritional provision.

This study evaluated SGA, symptoms and blood nutritional indicators in pancreaticobiliary tumor patients and explored the association in order to better understand the nutritional metabolism disorders and improve the quality of life of these patients.

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Keywords: Subjective global assessment; Symptoms; Blood nutritional indicators Inflammation; Obstructive jaundice; Pancreaticobiliary tumor patients

MATERIALS AND METHODS

Patients and data collection

This was a cross-sectional study included consecutive patients with pancreaticobiliary tumor admitted to surgical wards during an 8-month study period. Patients aged above 18 years and willing to give their informed consent were included. We excluded patients who were significant edema, pregnant, critically unstable condition, with severe endocrine disease, nephrotic syndrome and protein-losing enteropathies. Diagnose, sex, age, BMI, comorbidities (diabetes mellitus, hypertension and cardiopathy) and cancer stage were collected. Blood routine, liver and kidney function, pancreatic enzymes, serum tumor markers (CA19-9, CA125, CA72-4), CRP, blood nutritional indicators (serum protein Alb, PA, Tf, RBP, and folic acid, vit B12, vit A, vit E, vit K, vit D, iron, zinc and copper), SGA, PG-SGA and symptom (fatigue, nausea/vomiting, diarrhea, constipation, abdominal distension, anorexia, insomnia and pain) were collected on admission. Patients were followed up until discharged from hospital.

This study was a part of Nutrition Status and Clinical Outcome of Patients with Common Cancers in China (INSCOC) study which got the approval from Medical Ethics Committee of the First Affiliated Hospital of Sun Yat-sen University on May 7th 2013. Approval Code: [2013]82code. Registration number: ChiCTR1800020329. All the procedures conformed to the principles stated in INSCOC study Xu et al. (2020). All the procedures involving human samples conformed to the principles outlined in the Declaration of Helsinki. Informed consent in this study was obtained from all the patients before specimen collection.

Nutritional status and symptom assessment

SGA and PG-SGA which include weight loss, changes in dietary intake, metabolic stress, gastrointestinal symptoms, functional capacity and physical examination were performed as previously Chen et al. (2015). For SGA: scored A=well nourished; scored B=moderate malnutrition; scored C= severe malnutrition. For PG-SGA: scored 0-3 = well nourished; scored 4-8= moderate malnutrition; scored ≥9 = severe malnutrition. Symptom assessments were classified into 4 groups: no symptom = 0; a litter = 1; moderate =2; severe =3.

Laboratory methods

All measurements were carried out in the Department of Laboratory Medicine, Tongji Hospital of Tongji Medical College in Huazhong University of Science &Technology. PA, Tf, RBP, CPR, folic acid and vitB12 were determined on serum by latex enhanced immuno-turbidimetry method on the Roche Cobas 800 modular analyzer (Roche Diagnostic GmbH, Mannheim, Germany).

Plasma vitamin A (retinol), vitamin E (a-tocopherol), vitamin D (25-hydroxyvitamin D), and vitamin K1 (phylloquinone) were measured by high-performance liquid chromatography-tandem mass spectrometry on a ABsciex Qtrap 5500 coupled to an Exion LC system (Applied Biosystems, Foster City, CA, USA); Intra-assay imprecision was <5.10%. Iron, zinc and copper were determined on serum by a quadrupole inductively coupled plasma mass spectrometer (ICP-MS) equipped with a concentric glass nebulizer and a cyclonic spray chamber (7700x ICP-MS system, Agilent Technologies, CA, USA) and analyses were performed as previously Zeng et al. (2019).

Normal ranges for laboratory indexes

Laboratory indexes were obtained from the medical records of patients and measured by the Department of Clinical Laboratory. Normal ranges for these indexes were listed as following: 115/130–150/175 g/l for Hb; 1.1–3.2 × 10^9/l for Lmy; 45/59-84/104 μmol/l for Cr; 0.45–1.70mmol/l for TG; 2.9–5.2 mmol/l for TC; 20-35g/l for globulin; 35-52g/l for Alb; 200-400mg/l for PA; 2.00-3.60 g/l for Tf; 25-70mg/l for RBP; ≥4.0ng/ml for folic acid; 180-914 pg/ml for vitB12;407-1256 ng/ml for vit A;0.4-7.6ng/ml for vit K1; 8-32 ng/ml for vit D; 6.7-25.4 μg/ml for vit E;380.8-572.3 mg/l for iron; 4.8-9.3 mg/l for zinc; 664-1046 ug/l for copper; <2 mg/l for CRP; ≤21 umol/l for total bilirubin; ≤34 U/ml for CA19-9; ≤35 U/ml for CA125; ≤6.9 U/ml for CA72-4. Deficiency was defined as below the normal range; excess was defined as above the normal range.

Statistical analysis

Continuous variables were expressed as means ± SD and analyzed by variance analysis. Categorical variables were expressed as percentages and analyzed by chi-square tests or Fisher's exact tests. For ordered categorical proportion, Kruskal-Wallis test was used. Multiple ordered logistic regression, multivariate logistic regression and linear regression analysis were used for analysis. In analyses of the effects of CRP and disease stage on symptom severity by multiple ordered logistic regression, tumor stage and CRP were entered as the independent variables which were classified and converted to numerical equivalents as same as the followed. In analyses of the effects of CRP, SGA and obstructive jaundice on blood nutritional indicators by multivariate logistic regression and linear regression analysis, the independent variables were classified and converted to numerical equivalents as followed. Age: age < 60 years = 0; 60-70 years old = 1;> 70 years old = 2. Gender: woman=0, man=1. Tumor stage: benign tumor=0; stage I-II cancer=1; stage III-IV cancer=2. Total bilirubin: normal = 0;21-100umol/l = 1; >100umol/l = 2. CRP: <2 mg/l = 0; 2 mg/l ≤CRP ≤10

mg/l = 1; ＞10 mg/l = 2. SGA-A = 0; SGA-B = 1; SGA-C = 2. All analyses were performed with SPSS 17.0. Results were considered statistically significant if P < 0.05.

RESULTS

Patients' baseline characteristics and their associations with SGA

A total of 153 patients who had mean BMI of 21.58 ± 2.7 kg/m2 (range:15.06–32.30 kg/m2) and mean age of 60.4 ± 11.1y (range: 18–83 y) were finally studied. Among them, 13.1% were benign tumor, 86.9% were cancer. For cancer patients: 34.6% were biliary tract cancer, 17.3% were periampullary cancer and 48.1% were pancreatic cancer; 35.3% did radical operation and were diagnosed based on pTNM stage, the remainder were based on clinical staging (cTNM). Patients' baseline characteristics were exhibited by component ratio (Table 1). By chi-square tests: patients with older age, advanced tumor stage, elevated CRP, elevated transaminase, elevated bilirubin, elevated CA 19-9 and elevated CA 125 had higher malnutrition rates (Figure 1). After adjusting for other confounding factors, tumor stage, CRP and CA 19-9 were significantly associated with malnutrition by SGA (Table 2).

Figure 1: Comparison of malnutrition rates in different groups based on baseline characteristics (%). # indicated statistically significant difference P ＜0.05.

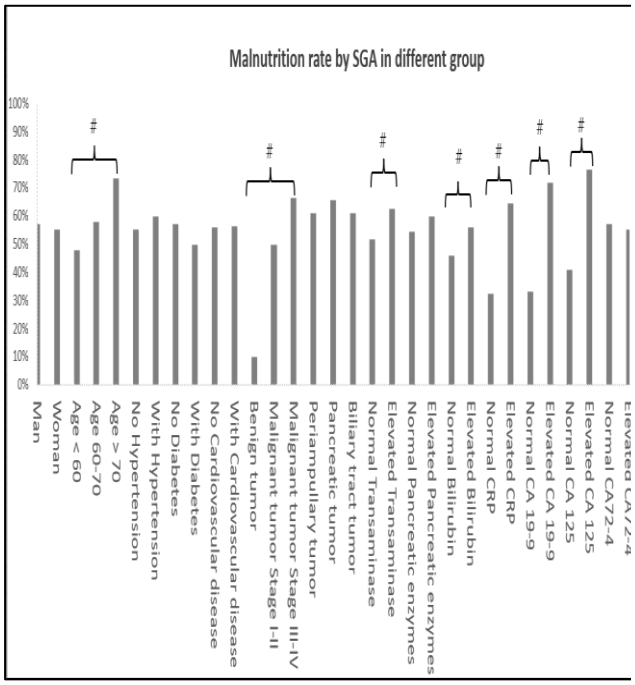


Table 1: Patients' baseline characteristics exhibited by component ratio (%)

Parameters	Total（n)	Classification (component ratio)		
Sex	153	Male (55.1%)	Female (44.9%)	
Age	153	＜60 years old (46.2%)	60-70 years old (34.0%)	＞70 years old (19.9%)
BMI	153	13.80% (＜18.5kg/m2)	86.20% (≥18.5 kg/m2)	
Weight loss recently	153	0%＜loss＜5% (14.4%)	5%-10% (25.5%)	＞10% (28.1%)
Intake reduction	153	25-50% (12.4%)	50%-75%(20.9%)	＞75%(29.4%)
SGA	153	A (43.8%)	B (39.9%)	C (16.3%)
PG-SGA	153	0-3 (32%)	4-8 (14.4%)	≥9 (53.6%)
CRP	147	<2 mg/l (34.7%)	2 mg/l -10 mg/l (33.3%)	＞10 mg/l (32.0%)
Tumor stage	153	benign tumor (13.1%)	stage I-II (17.00%)	stage III-IV (69.9%)
Hypertension	153	No (76.9%)	With (23.1%)	
Diabetes	153	No (86.5%)	With (14.4%)	
cardiovascular disease	153	No (89.5%)	With (10.5%)	
pancreatic enzymes	124	Normal (63.7%)	Elevated (36.3%)	
Transaminase	147	Normal (58.2%)	Elevated (48.1%)	
Bilirubin	148	Normal (56.9%)	21-100umol/l (13.7%)	>100umol/l (29.4%)
CA 72-4	120	Normal (68.3%)	Elevated (31.7%)	
CA 19-9	136	Normal (39.7%)	Elevated (60.3%)	
CA 125	118	Normal (60.2%)	Elevated (39.8%)	

Table 2: Univariate and multivariate logistic regressions identify the associated factors with malnutrition by SGA

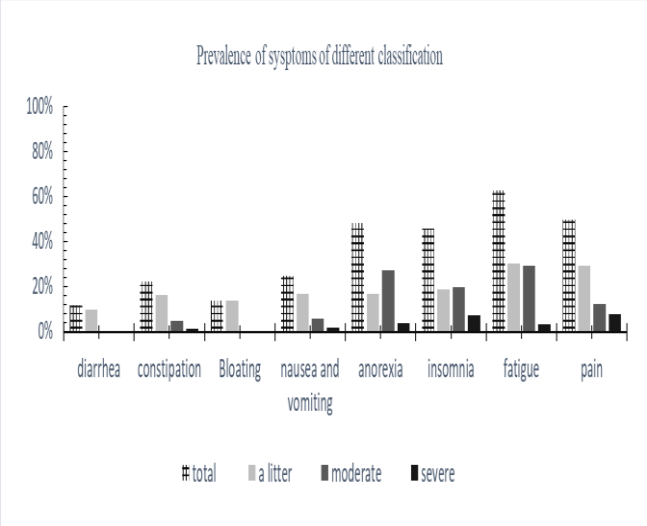
Variables	Crude OR (95% CI)	P	Adjusted OR (95% CI)	P
Age	1.68 (1.09-2.60)	0.02	—	—
Tumor stage	3.12 (1.87-5.51)	0	2.26 (1.02-5.02)	0.032
CRP	2.93 (1.84-4.66)	0	2.56 (1.45-4.54)	0.001
Total bilirubin	1.88 (1.27-2.77)	0.002	—	—
CA 19-9	5.13 (2.44-10.79)	0	3.37 (1.34-8.48)	0.009
CA125	4.74 (2.08-10.81)	0	—	—

— indicated P≥0.05.

Prevalence of symptoms of different severity and its association with disease stage and CRP.

In these patients, the most common symptom was fatigue, followed by pain, anorexia, insomnia, nausea/vomiting, constipation, abdominal distension and diarrhea (Figure 2).

Figure 2: Prevalence of symptoms of different severity.



Kruskal-Wallis test showed that: tumor stage was significantly associated with fatigue, pain, anorexia, insomnia and constipation (Figure 3); CRP was significantly associated with fatigue, pain, anorexia, insomnia, nausea/vomiting and constipation (Figure 4). By multiple ordered logistic regression, both CRP and tumor stage contributed to the severity of fatigue, pain and anorexia (Table 3).

The effects of CRP, SGA and obstructive jaundice on numerical value of blood nutritional indicators analyzed by multivariate linear regression analysis.

In table 4, Constant represents serum level of blood nutritional indicators when independent variables all scored 0. Unstandardized coefficient represents the change of serum level of blood nutritional indicators with each increased score of the independent variable. The negative number means the change of decrease and the positive number means the change of increase.

Figure 3: Score of fatigue, pain, anorexia, insomnia and constipation significantly differed among different tumor stages.

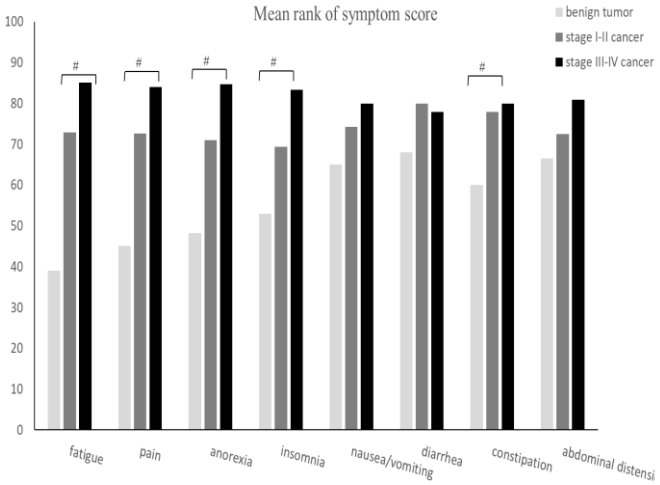


Figure 4: Score of fatigue, pain, anorexia, insomnia, nausea/vomiting and constipation significantly differed among different CRP groups.

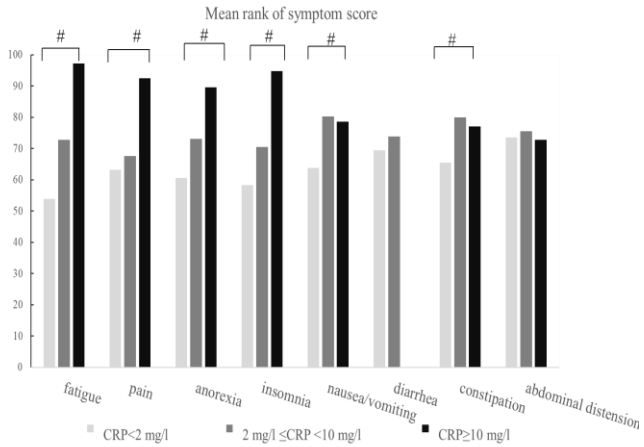


Table 3: Association of symptom severity with tumor stage and CRP by multiple ordered logistic regression.

dependent variables	independent variables	β	Exp (β)and 95% CI	P
Fatigue	Tumor stage	0.393	1.48 (1.08-2.02)	0.013
	CRP	0.564	1.76 (1.37-2.25)	0
Pain	Tumor stage	0.452	1.57 (1.13-2.18)	0.007
	CRP	0.295	1.34 (1.05-1.72)	0.019
Anorexia	Tumor stage	0.432	1.54 (1.10-2.15)	0.012
	CRP	0.366	1.44 (1.18-1.86)	0.005

Old age was associated with decrease of Alb, PA and Tf. Men was associated with decrease of Lmy, folate and TC, and increase of Hb, Cr and vit D. Advanced tumor stage was associated with increase of vit B12.With each increased score of CRP, Hb decreased by 4.5 %, Alb by 4.5%, PA by 13.8%, Tf by 7.2%, RBP by 16.5%, vit A by 18.3%, vit D by 15.6%, iron by 5.2 %, zinc by 3.1%, and globulin increased by 7.6% and copper by 19.8%; with each increased score of SGA, Lmy decreased by 9.6%, Hb by 3.7%, Alb by 2.0%, PA by 6.1% and Tf by 3.8%; with each increased score of bilirubin, Cr decreased by 7.9%, Alb by 2.1%, vit D by 15.6% and TC increased by 20.2%, TG by 75.7%, VitB12 by 176.4% and copper by 11.0% (Table 4).

Incidence of deficiency and excess of blood nutritional indicators.

Figure 5 showed the incidence of deficiency and excess of blood nutritional biomarker of the total. Lmy was affected by SGA. Deficiency of Lmy in SGA-A, SGA-B and SGA-C patients was 19.5%, 49.2% and 68% respectively. Hb, Alb, PA, Tf and RBP were affected by both CRP and SGA. In normal CRP and SGA-A patients, Alb deficiency was lowest (3.2%), followed by PA (22.6%), Tf (25.8%), RBP (32.2%) and Hb (48.4%), while in elevated CRP and SGA-(B+C) patients, these deficiencies were highest (Figure 6). Cr, TC and TG were affected by bilirubin. Cr deficiency was significantly higher in elevated bilirubin patients (25.8% versus 6.9%). TC and TG excesses were significantly higher in elevated bilirubin patients (39.4% versus 9.2% for TC and 61.5% versus 17.7% for TG). Globulin was affected by CRP. 3.9% of normal CRP patients and 15.6% of elevated CRP patients had elevated globulin.

The cut-off of vit A deficiency (< 407 ng/ml) in our hospital laboratory is higher than acknowledged standard (< 200 ng/ml). This led to the high deficiency rate (75% of the total). For vit A deficiency according to < 200 ng/ml,20.7% of the total, 0% of both RBP and CRP normal patients,5.6% of low RBP and normal CRP patients,7.1% of normal RBP and elevated CRP patients, and 52.0% of low RBP and elevated CRP patients had vit A deficiency. For vit D,86.2% had 25(OH)D < 20 ng/ml and 96.6% < 30 ng/ml.

Figure 5: The incidence of deficiency and excess of blood nutritional biomarker of the total. Abbreviations: D, deficiency; E, excess.

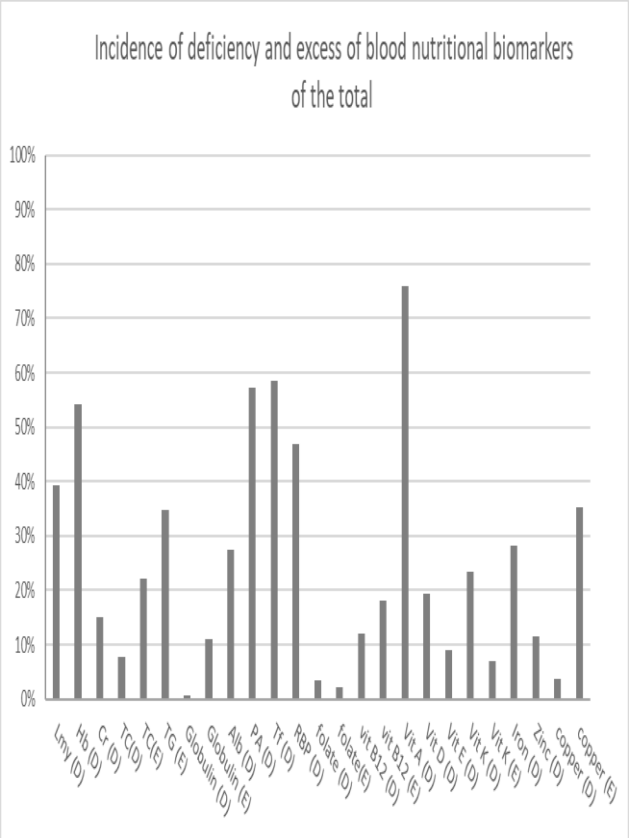


Table 4: Multivariate linear regression analysis for the effects of CRP, SGA and obstructive jaundice on blood nutritional indicators numerical value.

Biomarker	N	Constant	Unstandardized coefficient (standardized coefficient)					
			Age	Gender	Tumor stage	CRP	SGA	Total bilirubin
Lmy	153	2.05	—	-0.23 (-0.20)	—	—	-0.20 (-0.25)	—
HB	153	119.24	—	7.61 (0.21)	—	-5.35 (-0.24)	-4.41 (-0.17)	—
Cr	153	48.08	—	14.27 (0.52)	—	—	—	-3.78 (-0.25)
Alb	153	44.58	-1.07 (-0.18)	—	—	-2.02 (-0.36)	-1.15 (-0.18)	-0.96 (-0.19)
PA	145	273.96	-16.52 (-0.19)	—	—	-37.78 (-0.48)	-16.78 (-0.19)	—
Tf	145	2.63	-0.16 (-0.28)	—	—	-0.19 (-0.36)	-0.10 (-0.17)	—
RBP	145	30.69	—	—	—	-5.05 (-0.42)	—	—
Folate	143	15.67	—	-3.33 (-0.35)	—	—	—	—
Vit A	145	386.23	—	—	—	-70.58 (-0.44)	—	—
Vit D	145	13.87	—	3.34 (0.24)	—	- 2.16 (-0.25)	—	-1.86 (-0.24)
Iron	139	429.74	—	—	—	-22.24 (-0.25)	—	—
Zinc	139	5.89	—	—	—	-0.18 (-0.18)	—	—
Globulin	153	27.81	—	—	—	2.12 (0.33)	—	—
TC	153	4.5	—	-0.99 (-0.23)	—	—	—	0.91 (0.38)
TG	101	0.713	—	—	—	—	—	0.54 (0.48)
vit B12	143	62.86	—	—	110.89 (0.19)	—	—	104.16 (0.23)
Copper	139	719.25	—	—	—	142.06 (0.48)	—	78.86 (0.29)

—: indicated P≥0.05 and without unstandardized coefficient /standardized coefficient.

Figure 6: The incidences of deficiencies of Hb, Alb, PA, Tf and RBP in different groups based on CRP and SGA.

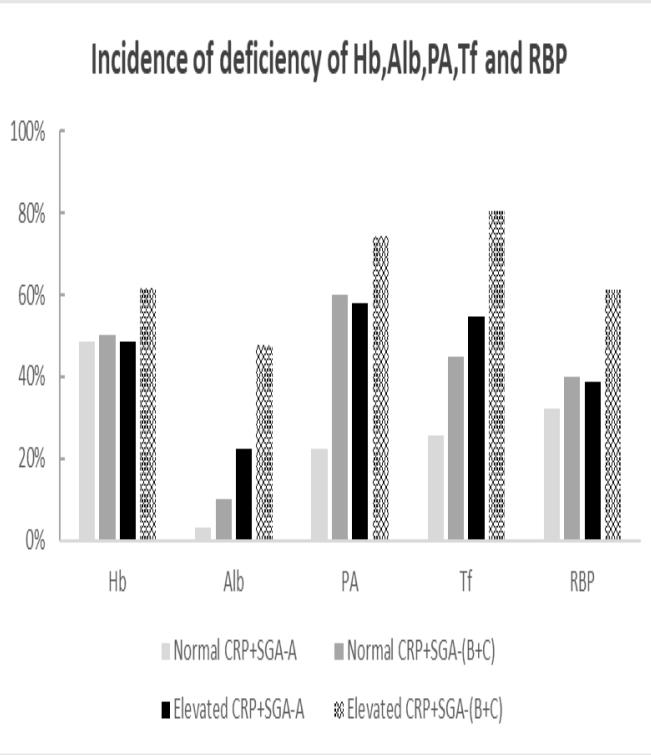
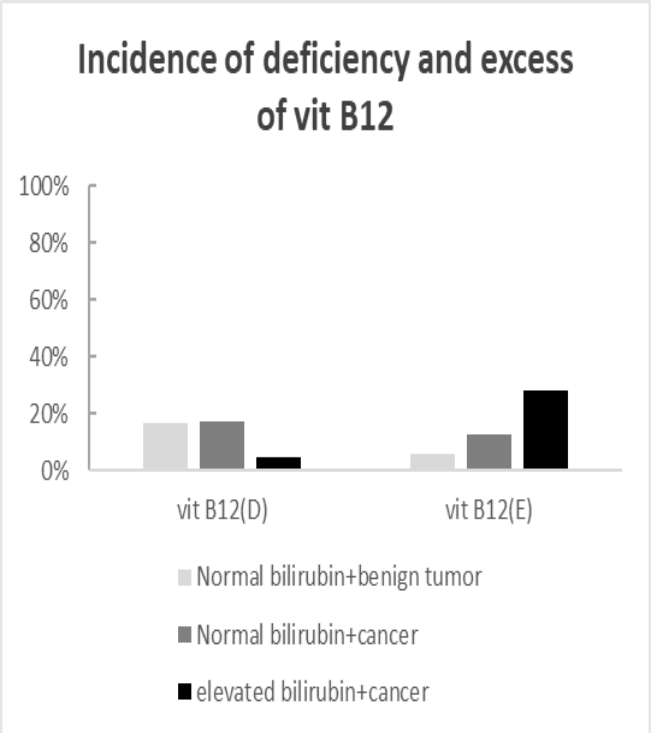


Figure 7: The incidence of deficiency and excess of vit B12 in different groups based on bilirubin and tumor stage. Abbreviations: D, deficiency; E, excess.



Vit K deficiency significantly increased with elevated bilirubin after adjusting age, gender, tumor stage, CRP and SGA by multivariate logistic regression (10.8% in normal bilirubin patients versus 40.3% in elevated bilirubin patients).Folate deficiency was rare; Vit B12 was affected by bilirubin and tumor stage. Elevated vit B12 was most common in elevated bilirubin cancer patients (Figure 7). For micro-nutrients, iron and zinc deficiencies were significantly higher with elevated CRP (34.1% versus 18.0% for iron and 13.6% versus 8.0% for zinc). Copper deficiency (10%) was only observed in normal CRP and bilirubin patients and no copper excess was observed in these patients. About 30% copper excess was observed in elevated CRP or elevated bilirubin patients. Copper excess (61.7%) was most observed in elevated CRP and elevated bilirubin patients.

DISCUSSIONS

Jikuan Jin et al. (2021) and I. Santos et al. (2021) respectively demonstrated 77.1% of ampullary carcinoma and 82.9% of pancreatic cancer were malnutrition by PG-SGA. This study confirmed the high malnutrition rate in this population. We failed to demonstrate the different malnutrition rates in different location of pancreaticobiliary cancer which may due to the small size of this study. SGA was chosen as nutrition status indicator in this study for the stronger and more stable association with blood nutritional indicators compared with PG-SGA. This may be due to that PG-SGA score is easily influenced by subjective symptoms while SGA relies largely on weight loss, changes in dietary intake and BMI and are more objective and stable. This study demonstrated that independent of advanced tumor stage, elevated CRP and CA 19-9 were risk factors for malnutrition by SGA. Inflammatory factors play an important role in the activation of catabolic processes such as lipolysis, proteolysis and increased resting energy expenditure might causing the malnutrition Flores et al. (1989). CA19-9 can accelerate pancreatic cancer progression by glycosylating proteins, binding to E-selectin, and strengthening angiogenesis and it was a significant predictor of poor prognosis Luo et al. (2021). This study demonstrated that CA19-9 was significantly associated with poor nutrition status. Pancreaticobiliary tumor patients with high CRP and CA19-9 should be paid more attention for nutrition support. Several studies had demonstrated the relationship between CRP level and weight loss/fatigue by univariate analysis, they failed to demonstrate the relationship with anorexia and pain Scott et al. (2003), Brown et al. (2005). This study demonstrated the relationships of CRP with fatigue, anorexia and pain independent of tumor stage. It underscored the significance of alleviating system inflammation to improve the nutritional status and living quality.

In normal CRP and well-nourished patients, serum Alb deficiency was seldom (3.2%) while PA, Tf, RBP and Hb

deficiency reached 22%-49%. This indicated that Alb is mainly influenced by inflammation and nutrition, but Tf, RBP and Hb are not. Inflammation played more important role than malnutrition in lowering serum Hb, Alb, PA, Tf and RBP in this population by comparing standardized coefficient in linear regression analysis. This study warned the high incidences of low Hb, PA, Tf and RBP (nearly 70%) in patients with both inflammation and malnutrition. We confirmed that Alb decreased with age which had been demonstrated before Weaving et al. (2016), Tf and PA were also demonstrated to be decreased with age which might be caused by decreased synthesis with age. RBP is degraded in kidney tubules. We speculated that RBP synthesis also decreased with age and RBP degradation by kidney also decreased with age. The decreased synthesis and decreased degradation offset each other and caused the unchanged serum RBP with age. Lym was only affected by SGA indicated that it was a specific nutritional maker in these patients. Lym deficiency was nearly 40% which was higher than general hospitalized patients (11.3%) Chen et al. (2015) and confirmed the higher incidence of hypo-immunity state in these patients especially in SGA-C patients (68%). Lym are relative lower in men. It had been showed that males had higher immunosuppression, maybe due to androgens; the greater female immunoreactivity, likely related to estrogens, lead to a greater resilience to infections but also to a higher risk for autoimmunity Dodd et al. (2022). Creatine is synthesized in liver. Production of creatine decreased in severe hepatic disease Cocchetto et al. (1983). Negative effect of obstructive jaundice on serum creatine was confirmed in this study and demonstrated that creatine was unreliable muscle biomarker in liver disease. Obstructive jaundice cause hyperlipemia which is related to lipoprotein X and this kind of hyperlipemia should not be treated with statins Nemes et al. (2016). Our study further confirmed hyperlipemia by obstructive jaundice and the effect is especially great on TG.

According to acknowledged standard of vit A deficiency (<200 ng/ml), no deficiency was observed in patients of well-nourished and without inflammation. Low RBP would suppress vit A secretion from liver and caused the low serum retinol level Fujita et al. (2009). The negative effect of inflammation on vit A might for its negative effect on RBP. According to acknowledged standard, 86.2% had 25(OH)D < 20 ng/m. It indicated that vit D deficiency was pandemic. Vit E deficiency was 9.0% which was higher than that of urban adults of Wuhan (0.47%) Shen et al. (2023). Our vit E deficiency standard (6.7ug/ml) is higher than the acknowledged (5ug/ml). However, the hyperlipidemia in our study may underestimate the vit E deficiency Berger et al. (2022). Deficiency rate of vit K1 was high (near 40%) in patients with obstructive jaundice in this study. Jennifer Stropl reported 48% vitamin K deficiency (measurement of undercarboxylated vitamin K-dependent proteins) in children with cholestatic liver disease Strople et al. (2009). Measurement of undercarboxylated vitamin K-dependent proteins is more sensitive than serum vitk1 and not affected by recent dietary intake Hathaway et al. (1993). Results of this study showed that obstructive jaundice negatively affected vit D and vit K but not vit A and vit E. We supposed that vit K is stored in body only in small amount and vulnerable to deficiency when faced inadequate bile-dependent intestinal absorption in obstructive jaundice. Vit D is metabolized to 25-OHD in liver, under obstructive jaundice, this function is impaired and causing the vit D vulnerable to deficiency.

Patients with cancer were reported 7% folate deficiency in USA, considerably higher than the general population Epstein-Peterson et al. (2021). Folate deficiency was low (3.5%) even in patients with pancreaticobiliary tumor in this study. We speculated that the rich leafy green vegetables provision for Chinese caused the low deficiency. Vit B12 deficiency was higher than folate might for the reason that the vit B12 is mainly in animal food which is difficult to be digested by patients with pancreaticobiliary tumor. In addition, absorption of vit B12 is impaired for the insufficient degradation of haptocorrin-vitB12 complex by pancreatic enzymes under obstructive jaundice to make it available to intrinsic factor Shipton et al. (2015). This study further confirmed that vit B12 elevation in malignancies and obstructive jaundice. The mechanisms of the increase of serum vitB12 would for the increased vitB12 carriers produced by immune cells or hepatic cells or increased release of vitB12 by injured hepatic cells Andrès et al. (2013). However, the increases were due to metabolically inert transcobalamin I and III, metabolically active transcobalamin II was repressed Andrès et al. (2013). High vitB12 level would indicate a need for further measurements of metabolites including methylmalonic acid and homocysteine to confirm functional deficiency Andrès et al. (2013).

Iron and zinc are negatively affected by inflammation. Intravenous therapy of micronutrient could not correct the deficiency and instead increase the risk of infections in acute infection Jiang et al. (1985), Sobocinski et al. (1977). More studies are needed to set new cut-off value under inflammation. There would be no benefit to supply if the low level is caused by inflammation while they store was enough. Serum copper increased by inflammation and cholestasis for the increased carrier (ceruloplasmin) and decrease copper excretion. Patients with obstructive jaundice should be given less copper.

Our study had limitations. Firstly, clinical manifestations of micronutrient abnormity of these patients were not collected to verify the consistency with serum level. Secondly, functional analyses of micronutrient were not performed to better understand the abnormity of serum micronutrient. Thirdly, some nutritional biomarkers are

not normal distribution and would better to be transformed into normal distribution in multivariate linear regression analysis. We thought the non-transformed data more intuitively exhibited the influence of the related factors although the regression equations were not suited to be extrapolated. Fourthly, size in our study is small.

In summary, the results of the current study indicated that: pancreaticobiliary tumor patients with advanced tumor stage, elevated CRP and CA 19-9 should be paid more attention for malnutrition. Inflammation should be controlled to relieve the fatigue, anorexia and pain. Old patients are more susceptible to serum protein deficiency. Men are more susceptible to folic acid and lym deficiency, and less likely to had vit D deficiency and hyperlipemia. Cancer can cause high vitB12. Inflammation overestimates the deficiency of Alb, PA, Tf , RBP vit A, vit D, iron and zinc and underestimates the deficiency of globulin and copper. Malnutrition by SGA increases the deficiency of Lym and serum protein but does not influences micro-nutrients. Obstructive jaundice increases the risk of Cr, Alb, vit D, and vit K deficiency, and cause high serum level of vitB12, hyperlipemia, and copper accumulation. More researches are needed to explore the effects of related factors on metabolism of these biomarkers in the future to develop specific nutritional support strategy.

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REFERENCES

1.Gilliland TM, Villafane-Ferriol N, Shah KP, et al. 2017 Mar 7. Nutritional and Metabolic Derangements in Pancreatic Cancer and Pancreatic Resection.Nutrients.9(3):243.

2.Jin J, Xiong G, Wang X, et al. 2021 Nov 30. The Impact of Preoperative and Postoperative Malnutrition on Outcomes for Ampullary Carcinoma After Pancreaticoduodenectomy. Front Oncol.11:748341.

3.Bye A, Jordhøy MS, Skjegstad G, et al. 2013 Jan. Symptoms in advanced pancreatic cancer are of importance for energy intake. Support Care Cancer.21(1):219-27.

4.Detsky AS, McLaughlin JR, Baker JP, et al. 1987 Jan-Feb. What is subjective global assessment of nutritional status? JPEN J Parenter Enteral Nutr.11(1):8-13.

5.Bauer J, Capra S, Ferguson M. 2002 Aug. Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. Eur J Clin Nutr.56(8):779-85.

6.Wirth JP, Rajabov T, Petry N, et al. 2018 Oct 11. Micronutrient Deficiencies, Over- and Undernutrition, and Their Contribution to Anemia in Azerbaijani Preschool Children and Non-Pregnant Women of Reproductive Age. Nutrients.10(10):1483.

7.Neves Wd, Alves CRR, Borges APDS, et al. 2021 Apr 12. Serum Creatinine as a Potential Biomarker of Skeletal Muscle Atrophy in Non-small Cell Lung Cancer Patients. Front Physiol.12:625417.

8.Zhang K, Qin W, Zheng Y, et al. 2022 Jan 6. Malnutrition Contributes to Low Lymphocyte Count in Early-Stage Coronavirus Disease-2019. Front Nutr.8:739216.

9.Nakamura Y, Motokawa M. 2000 Feb 29. Hypolipemia associated with the wasting condition of rabbits infected with Strongyloides papillosus. Vet Parasitol.88(1-2):147-51.

10.Xu H, Song C, Wang C, et al. 2020.Investigation on nutrition status and clinical outcome of patients with common cancers in Chinese patients: a multicenter prospective study protocol. Int J Clin Trials. 7(2):94–102.

11.Z Y Chen, C Gao,T Ye, et al. 2015 May. Association between nutritional risk and routine clinical laboratory measurements and adverse outcomes: a prospective study in hospitalized patients of Wuhan Tongji Hospital. Eur J Clin Nutr.69(5):552-7.

12.Zeng H-L, Li H, Lu J, et al. 2019 Jun.Assessment of 12 Metals and Metalloids in Blood of General Populations Living in Wuhan of China by ICP-MS. Biol Trace Elem Res.189(2):344-353.

13.Santos I, Mendes L, Mansinho H, et al. 2021 Nov.Nutritional status and functional status of the pancreatic cancer patients and the impact of adjacent symptoms. Clin Nutr.40(11):5486-5493.

14.Flores EA, Bistrian BR, Pomposelli JJ, et al.1989 May.Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. J Clin Invest.83(5):1614-22.

15.Luo G, Jin K, Deng S, et al. 2021 Apr.Roles of CA19-9 in pancreatic cancer: Biomarker, predictor and promoter.Biochim Biophys Acta Rev Cancer.1875(2):188409.

16.Scott HR, McMillan DC, Brown DJ F, et al. 2003 Jun. A prospective study of the impact of weight loss and the systemic inflammatory response on quality of life in patients with inoperable non-small cell lung cancer. Lung Cancer .40(3):295-9.

17.Brown DJF, McMillan DC, Milroy R. 2005 Jan 15. The Correlation between Fatigue, Physical Function, the Systemic Inflammatory Response, and Psychological Distress in Patients with Advanced Lung Cancer. Cancer .103(2):377-82.

18.Weaving G, Batstone GF, Jones RG. 2016 Jan. Age and sex variation in serum albumin concentration: an observational study.Ann Clin Biochem.53(Pt 1):106-11.

19.Dodd KC, Menon M. 2022 Nov 24. Sex bias in lymphocytes: Implications for autoimmune diseases.Front Immunol.13:945762.

20.Cocchetto D M, Tschanz C, Bjornsson T D. 1983 Jun. Decreased rate of creatinine production in patients with hepatic disease: implications for estimation of creatinine clearance. Ther Drug Monit .5(2):161-8.

21.Nemes K, Åberg F, Gylling H, et al. 2016 Aug 8. Cholesterol metabolism in cholestatic liver disease and liver transplantation: From molecular mechanisms to clinical implications. World J Hepatol. 8(22):924-32.

22.Fujita M, Brindle E, Rocha A, et al. 2009 Jul. Assessment of the relative dose-response test based on serum retinol-binding protein instead of serum retinol in determining low hepatic vitamin A stores.Am J Clin Nutr .90(1):217-24.

23.Shen Y, Liu K, Luo X, et al. 2023 Mar 30. The low prevalence rate of vitamin E deficiency in urban adults of Wuhan from central China: findings from a single-center, cross-sectional study.Eur J Med Res.28(1):141.

24.Berger MM, Shenkin A, Schweinlin A, et al. 2022 Jun. ESPEN micronutrient guideline. Clin Nutr.41(6):1357-1424.

25.Strople J, Lovell G, Heubi J. 2009 Jul. Prevalence of subclinical vitamin K deficiency in cholestatic liver disease. J Pediatr Gastroenterol Nutr.49(1):78-84.

26.Hathaway WE. 1993.Vitamin K deficiency.Southeast Asian J Trop Med Public Health.24 Suppl 1:5-9.

27.Epstein-Peterson ZD, Chokshi I, Barrow B, et al. 2021 Aug.Laboratory evaluation of folate deficiency among inpatients with cancer. Int J Lab Hematol .43(4): O164-O167.

28.Shipton MJ, Thachil J. 2015 Apr.Vitamin B12 deficiency - A 21st century perspective.Clin Med (Lond).15(2):145-50.

29.Andrès E, Serraj K, Zhu J, et al.2013 Jun. The pathophysiology of elevated vitamin B12 in clinical practice.QJM.106(6):505-15.

30.Jiang Z, Yang NF, Jiao KS, et al. 1985 Mar-Apr. Post-operative fall in serum zinc concentrations is unaffected by intravenous zinc therapy. J Parenter Enteral Nutr. 9: 196-8

31.Sobocinski PZ, Canterbury WJ, Powanda MC. 1977 Nov. Differential effect of parenteral zinc on the course of various bacterial infections. Proc Soc Exp Biol Med.156: 334-9.

