Measurements of nutritional status and impact of malnutrition in polytrauma patients

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Chapter 4

The value of metabolites and vitamins for the assessment of nutritional status in hospitalized patients. A systematic review

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ABSTRACT

This systematic review aims to summarize the currently available literature regarding the association of plasma metabolites and vitamins with the nutritional status in adult hospitalized patients.

A systematic literature search was performed in PubMed and EMBASE, and all studies comparing metabolite or vitamin levels in malnourished versus well-nourished hospitalized patients were included. Twenty-three studies were eligible for inclusion, representing 3803 hospitalized patients.

Several metabolites involved in the metabolism of methionine, purine, glutathione, carnitine, phenylalanine, and tryptophan, as well as some vitamins, seem to be associated with malnutrition in hospitalized patients. These compounds can potentially be used to assess nutritional status.

INTRODUCTION

Malnutrition is the result of an imbalance between intake, uptake, and the required amount of macro- and micronutrients. This imbalance leads to an altered body composition and body cell mass which diminishes physical and mental function and impairs recovery from disease.[1] Together with the stress-related catabolism caused by inflammation, malnutrition increases the risk for impaired wound healing, infections, and organ dysfunction.[2] These complications can cause an increase in the inflammatory response and therefore result in further aggravation of malnutrition.[2,3] To break this vicious circle, it is essential to adequately diagnose malnutrition and prevent deterioration.

Research has shown that up to 50% of hospitalized patients are malnourished, depending on the definition used and population included.[2] Several tools to assess nutritional status have been developed, including nutritional screening tools, such as the Subjective Global Assessment (SGA), Patient-Generated Subjective Global Assessment (PG-SGA), Mini Nutritional Assessment (MNA), Nutritional Risk Screening (NRS-2002), and Malnutrition Universal Screening Tool (MUST), as well as visceral proteins, and anthropometric measures (height, weight, and body composition). Some of these screening tools were developed for specific populations; for example the MNA is designed to diagnose malnutrition in elderly patients, and the MUST and PG-SGA are validated for oncology patients.[4,5] However, there is still no gold standard for measuring nutritional status in all hospitalized patients.[6] The currently available nutritional screening tools include information on the history of a patient's weight and diet, which is not always available in clinical settings. The Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition described a standardized approach to identify adult malnutrition in routine clinical practice.[7] The criteria that a registered dietitian can obtain and document to support a diagnosis of malnutrition include energy intake, weight loss, and physical exam. Moreover, fluid resuscitation and edema influence weight, body circumferences, and other anthropometric measurements.[8] Additionally, visceral proteins (e.g. albumin, and pre-albumin) lack sensitivity as they are influenced by inflammation. During inflammatory states, the production of acute-phase proteins in the liver is increased and therefore the synthesis of visceral proteins is decreased regardless of nutritional status.[9]

A relatively new but promising method is the use of plasma metabolites and vitamins to assess nutritional status. Metabolites are intermediate- or end-products of biochemical pathways, such as glycolysis and citric acid cycle. Examples include sugars, amino acids, and nucleotides. Metabolites are considered to be biomarkers of several phenotypic states, and research suggests that metabolites can even act as controllers of the phenotype.[10] The metabolome is the global collection of all low-molecular-weight metabolites that are produced by cells during metabolism.[11] The human metabolome comprises over 100,000 metabolites and new metabolites continue to be added to the Human Metabolome Database (HMDB).[12] Because the metabolite composition is influenced by many processes in the body, changes in plasma metabolite levels may occur much earlier than any clinical symptoms. Metabolites have been considered as biomarkers for many diseases, such as pancreatic cancer, non-insulin dependent diabetes mellitus, and memory impairment.[13-15] Additionally, vitamins are related to a healthy diet and several vitamins are known to function as antioxidants. Since malnutrition is related to oxidative stress, the question arises whether vitamins might also be useful in diagnosing malnutrition.[16] The purpose of this study is to systematically review the body of published scientific evidence and summarize the value of plasma metabolites and vitamins as potential biomarkers for monitoring nutritional status in hospitalized patients.

METHODS

Search Strategy

This systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.[17] A literature search was performed in PubMed and EMBASE in collaboration with an experienced medical librarian in December 2021. The search strategy included synonyms and related terms for hospitalized patients, biomarkers, metabolites, vitamins, antioxidants, and nutritional status (**Appendix 1**).

Eligibility Criteria and Article Selection

Article selection was performed independently by two researchers (EAHV and JJJO). The titles and abstracts of identified studies were screened, using the following selection criteria: (1) the study included adult hospitalized patients, (2)

one or more plasma metabolites or vitamins were researched, (3) the nutritional status was assessed using a nutritional assessment/screening tool (e.g. SGA, MUST, or MNA), the Body Mass Index (BMI), or a combination of laboratory results and anthropometric measurements, and (4) the relationship between plasma metabolite/vitamin levels and nutritional status was evaluated. Articles that researched the nutritional status of patients after bariatric surgery were excluded. Publications in English, German, and Dutch were selected, between 1952 and 2021. The full-text of potentially eligible articles were read, and included when all the inclusion criteria were met. The reference lists of the included articles were screened for additional literature.

Data Extraction and Risk of Bias Assessment

Data extraction and risk of bias assessment were performed independently by the same two researchers (EAHV and JJJO). Data on study characteristics (study design, country, participants (number, mean age, sex), applied nutritional assessment tool, researched biomarker(s)), and study results (percentage of malnourished patients, metabolite levels, and their association) were extracted from the articles.

The risk of bias in the selected studies was assessed according to the Methodological Index for Non-Randomized Studies (MINORS) criteria, which includes 12 items for comparative studies and 8 items for non-comparative studies that are scored as 0 (not reported), 1 (reported but inadequate), or 2 (adequately reported). The maximum score is 16 for non-comparative studies and 24 for comparative studies.[18]

RESULTS

Selection of Articles

The literature search identified 936 studies in PubMed and 126 studies in Embase. 1006 records were screened after duplicate removal. 851 articles were excluded based on title and abstract. Three articles were added after hand search of the reference lists. After reading the full-text articles of the remaining 158 studies, 135 studies were excluded for various reasons (**Figure 1**). Relevant data from the twenty-three included studies are summarized in **Table 1**.

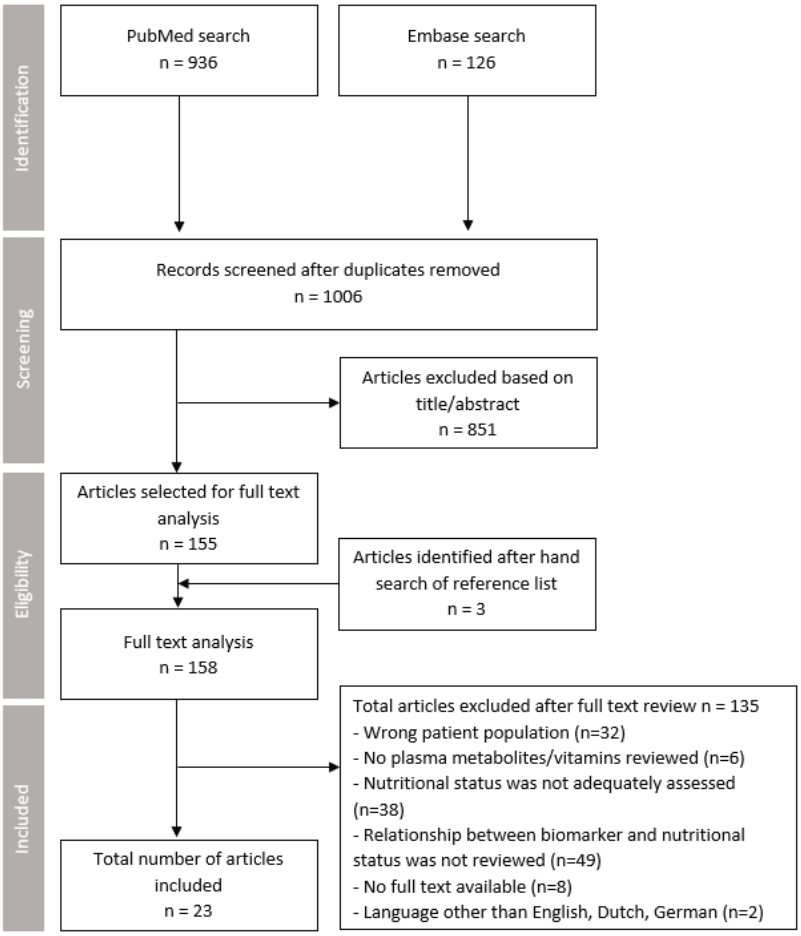

Figure 1: Studies resulting from literature search with reason for exclusion

Risk of Bias

Risk of bias of the included studies was assessed, using the MINORS-criteria, as low (total score ≥20 out of 24) for the studies by Chou et al,[19] Katić et al,[20] Tas Kilic et al,[21] Ramel et al,[22] and Vosoughi et al,[23] and moderate (total score 15-19 out of 24) for the other studies (**Table 2**). In all studies, the assessment of study endpoints was potentially biased, as no study evaluated the study endpoints blindly. Additionally, only Chou et al[19] and Vosoughi et al[23] performed a sample size calculation or noted why the sample size calculation could not be performed. Two studies collected the data retrospectively, and therefore did not score the maximum of 2 points for prospective collection of data.[24,25]

Table 1: Study characteristics and outcomes

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Avelino et al [39]	Brazil	Prospective cohort	150	Patients admitted to the clinical and surgical wards	51	SGA A: 50 (±15); SGA B: 48 (±16); SGA C: 52 (±18)	No MN: SGA A Mild MN: SGA B Severe MN: SGA C	No MN: 50.7% (n=76) Mild MN: 25.3% (n=38) Severe MN: 24.0% (n=36)	VitC (mg/dL) and Creat (mg/dL) VitC deficiency: <0.4	No MN vs mild MN vs severe MN: VitC: 0.7 (0.1-1.5) vs 0.5 (0.2-1.3) vs 0.3 (0.0-0.9) (p<0.05) Creat: 0.9 (0.1-3.3) vs 0.9 (0.5-1.7) vs 0.9 (0.5-2.5) (p>0.05) Vitamin C deficiency (%) in No MN vs mild MN vs severe MN: 21.1 vs 34.2 vs 63.9 (p<0.05)
Christopher et al [32]	USA	Cross-sectional	210	Patients with newly diagnosed solid malignant tumor	62	<50 yrs: 19% (n=39) 50-69 yrs: 63% (n=133) ≥70 yrs: 18% (n=38)	No MN: PG-SGA A Mild MN: PG-SGA B Severe MN: PG-SGA C	No MN: 39.7% (n=83) Mild MN: 36.4% (n=76) Severe MN: 23.9% (n=50)	25(OH)D (ng/mL): Suboptimal: <30 (n=131) Optimal: 30-80 (n=79)	Suboptimal vs optimal 25(OH)D levels: No MN: 36.9% (n=48) vs 44.3% (n=35); Mild MN: 36.9% (n=48) vs 35.4% (n=28); Severe MN: 26.2% (n=34) vs 20.3% (n=16) Suboptimal 25(OH)D: No MN: OR=1**; Mild MN: OR=0.97** (95% CI 0.48-1.95); Severe MN: OR=1.28** (95% CI 0.53-3.07)
Chou et al [19]	Taiwan	Prospective cohort	95	Mechanically ventilated patients with sepsis admitted to the medical ICU	61	70 (60-78)	No MN: NRS-2002 0-2 MN: NRS-2002 ≥ 3	-	TMAO (µmol/L) Low TMAO: <0.4 (n=32) Median TMAO: 0.4-2.5 (n=32) High TMAO: ≥ 2.5 (n=31)	NRS-2002 score in low TMAO vs median TMAO vs high TMAO: 5.0 (5.0-6.0) vs 4.0 (4.0-5.8) vs 4.0 (3.0-4.0) (p<0.001) Spearman correlation coefficient: r=-0.51 (p<0.001) Univariate linear regression: β=-0.453 (p<0.001)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Cunha et al [26]	Brazil	Cross-sectional	127	Elderly patients (≥65 yrs)	63	No MN: 72 (±6) MN: 74 (±7)	No MN: BMI ≥18.5 MN: BMI <18.5	No MN: 83.5% (n=106) MN: 16.5% (n=21)	VitA (µg/dL), VitC (mg/dL), VitE (µg/dL), Ct (µg/dL), and EGRAC Deficiencies: VitA ≤19; VitC <0.3; VitE <0.7; Ct <39; EGRAC >1.29	No MN vs MN: VitA: 41.9 (9.3-132.2) vs 39.6 (16.5-78.4); VitC: 0.3 (0.0-1.0) vs 0.2 (0.1-1.2); VitE: 1.0 (0.3-11.0) vs 1.0 (0.5-2.2); Ct: 106 (27.2-416.2) vs 121 (35.3-298.3); EGRAC: 1.3 (1.0-3.3) vs 1.4 (1.0-2.6) Deficiencies (%) in No MN vs MN: VitA: 29.6 vs 28.6 (p>0.05); VitC: 56.7 vs 80.9 (p<0.01); VitE: 25.0 vs 18.7 (p>0.05); Ct: 3.0 vs 14.3 (p<0.01); EGRAC: 56.2 vs 58.8 (p>0.05)
Djurasinovic et al [33]	Belgrade	Prospective cohort	133	Patients with lympho-proliferative malignancies	54	58 (18–84)	No MN: NRS-2002 0-2 MN: NRS-2002 ≥ 3	No MN: 54.9% (n=73) MN: 45.1% (n=60)	25(OH)D (nmol/L): SevDef: ≤25 (n=37); Def: 25-50 (n=80); Ins: 50-75 (n=12)	SevDef vs Def vs Ins: No MN: 37.8% (n=14) vs 60.0% (n=48) vs 68.8% (n=11); MN: 62.2% (n=23) vs 40.0% (n=32) vs 31.2% (n=5); (p=0.04)
Førli et al [36]	Norway	Cross-sectional	71	Patients with advanced pulmonary disease considered for lung transplantation	45	No MN: 52 (26-60) MN: 47 (25-60)	No MN: BMI 20-25 MN: BMI < 20	No MN: 40.8% (n=29) MN: 59.2% (n=42)	25(OH)D (nmol/L) and 1,25di(OH)D (pmol/L) 25(OH)D: Def: <37.5 Ins: 37.5-75	No MN vs MN: 25(OH)D: 37.2 (±15.7) vs 38.0 (±16.5) (p>0.05) 1,25di(OH)D: 82.4 (±30.6) vs 76.2 (±35.4) (p>0.05) Def: 55% (n=16) vs 52% (n=22) (p>0.05); Ins: 45% (n=13) vs 45% (n=19) (p>0.05)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Holden et al [37]	Canada	Cross-sectional	172	Patients with stage 3-5 chronic kidney disease	61	61 (±14)	No MN: SGA A Mild MN: SGA B Severe MN: SGA C	No MN: 79.3% (n=138) Mild MN: 20.7% (n=36) Severe MN: 0% (n=0)	VitK1 (nmol/L), %ucOC, PIVKA-II, 25(OH)D (nmol/L)	Spearman correlation coefficients for SGA: VitK1: r=0.11 (p=0.17) %ucOC: r=0.02 (p=0.79) PIVKA-II: r=0.08 (p=0.41) 25(OH)D: -0.08 (p=0.31)
Hosseini et al [27]	Iran	Cross-sectional	225	Patients >65 years with CHF and NYHA class III-IV	68	71 (±1)	No MN: MNA >23.5 Risk of MN: MNA 17-23.5 MN: MNA <17	No MN: 9.3% (n=21) Risk of MN: 80.9% (n=182) MN: 9.8% (n=22)	BUN (mmol/L)	No MN vs risk of MN vs MN: 24.9 (±8.1) vs 25.9 (±14.5) vs 24.9 (±9.2) (p=0.9)
Jatoi et al [40]	USA	Cross-sectional	27	Patients admitted to the Adult Gastro-enterology and General Internal Medicine services	41	46 (±16)	No MN: SA >3.5, ALC >1.5, BW ≥80% of ideal, and uWL <4.5 kg or <15% of BW in 3 months MN: At least one of SA, ALC, BW, uWL in abnormal range	No MN: 25.9% (n=7) MN: 74.1% (n=20)	VitK1 (nmol/L)	No MN vs MN: 0.25 (0.02-0.52) vs 0.19 (0.07-3.93) (p=0.73)
Katić et al [20]	Croatia	Cross-sectional	310 (298 are included in NA)	Patients with chronic graft-vs-host disease after allo-HSCT	55	48 (36-57)	No MN: PG-SGA A Mild MN: PG-SGA B Severe MN: PG-SGA C	No MN: 65.8% (n=196) Mild MN: 28.2% (n=84) Severe MN: 6.0% (n=18)	25(OH)D (ng/mL) Low: ≤20 (n=68) High: >20 (n=230)	No MN vs mild MN vs severe MN: Low: 19.4% (n=38) vs 23.8% (n=20) vs 55.6% (n=10); High: 80.6% (n=158) vs 76.2% (n=64) vs 44.4% (n=8); (p=0.004) No MN vs mild/severe MN: Low: 19.4% (n=38) vs 29.4% (n=30); High: 80.6% (n=158) vs 70.6% (n=72); (p=0.06)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Li et al[35]	China	Cross-sectional	82	Patients with fractures who had surgical treatment	27	70 (54–85)	No MN: NRS-2002 0-2 MN: NRS-2002 ≥ 3	No MN: 63.4% (n=52) MN: 36.6% (n=30)	25(OH)D (ng/mL), Ca (mmol/L), OC (ng/mL), PTH (pg/mL)	No MN vs MN: 25(OH)D: 26.5 (±1.2) vs 17.2 (±2.1) (p=0.00) OC: 3.7 (±0.5) vs 1.3 (±0.2) (p=0.00) Ca: 2.2 (±0.0) vs 2.2 (±0.1) (p=0.21) PTH: 21.0 (±2.1) vs 13.0 (±5.6) (p=0.12)
Mogensen et al[34]	USA	Prospective cohort	85	Patients with SIRS or sepsis admitted to the ICU	57	55 (±14)	No MN: WN or at risk for MN; MN: Diagnosis of (non)specific protein-calorie MN; Diagnosis was made by a registered dietician based on a combination of laboratory results and anthropometric measurements	No MN: 62% (n=53) MN: 38% (n=32)	281 metabolites	15 most predictive metabolites for MN: OH-PA VIP=2.61 Hx VIP=2.54 TML VIP=2.52 OH-PL VIP=2.45 NAM VIP=2.29 PyrGln VIP=2.29 Andros-S VIP=2.21 Kyn VIP=2.20 NAPhe VIP=2.12 MTA VIP=2.09 Urea VIP=2.05 P-GPA VIP=2.05 VitB3 VIP=2.02 S-GPA VIP=2.00 Cl VIP=1.98
										Linear regression coefficient

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
										MTA β=0.71 (p=0.01) P-GPA β=−0.63 (p=0.02) TML β=0.60 (p=0.02) VitB3 β=−0.70 (p=0.03) NAM β=0.51 (p=0.03) PyrGln β=0.49 (p=0.03) Val β=−0.60 (p=0.03) Hx β=0.46 (p=0.04) Kyn β=0.53 (p=0.04) PL β=0.32 (p=0.049) TrpB β=−0.33 (p=0.05) γ-GPA β=0.47 (p=0.06) OH-PL β=0.32 (p=0.07) 3-UPA β=0.37 (p=0.07) Urea β=0.42 (p=0.07)
Olvera-Soto et al[38]	Mexico	Cross-sectional	70	Patients aged 18-65 years with stage 4 Chronic Kidney Disease	46	47 (34-53)	No MN: SGA A Mild MN: SGA B Severe MN: SGA C	No MN: 67.1% (n=47) Mild MN: 25.7% (n=18) Severe MN: 7.1% (n=5)	25(OH)D (ng/mL) Suf: ≥30 (n=0) Ins: 20-30 (n=18) Def: 10-20 (n=36) SevDef: <10 (n=16)	Ins vs Def vs SevDef: No MN: 23.4% (n=11) vs 51.1% (n=24) vs 25.5% (n=12); (p=0.69) Mild MN: 33.3% (n=6) vs 50.0% (n=9) vs 16.7% (n=3); (p=0.68) Severe MN: 20% (n=1) vs 60% (n=3) vs 20% (n=1); (p=1.00)
Pourhassan et al[25]	Germany	Cross-sectional	233	Patients ≥ 60 years admitted to geriatric acute care ward	37	82 (±7)	No MN: MNA-SF 12-14 Risk of MN: MNA-SF 8-11 MN: MNA-SF 0-7	No MN: 14% (n=32) Risk of MN: 47% (n=106) MN: 39% (n=89)	VitB1 (ng/mL)	No MN vs risk of MN vs MN: 67.0 (±21.8) vs 64.5 (±18.8) vs 65.5 (±28.1) (p=0.45)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Ramel et al [28]	Iceland	Cross-sectional	60	Elderly patients >65 years	37	83 (±8)	No MN: less than 3/7 of parameters abnormal MN: at least 3/7 of parameters abnormal TSF <5th P; MAMC <5th P, BMI <20; TLC <1.82; SA <31; SPA <180; uWL >5%	No MN: 41.7% (n=25) MN: 58.3% (n=35)	VitB12 (pmol/L), FA (nmol/L), CysC (mg/L), HC (µmol/L)	No MN vs MN: VitB12: 597 (±367) vs 659 (±412) (p=0.56) FA: 19.7 (±12.1) vs 22.6 (±11.8) (p=0.36) CysC: 1.51 (±0.88) vs 1.62 (±0.55) (p=0.046) HC: 12.9 (±5.8) vs 14.1 (±6.7) (p=0.50)
Ramel et al [22]	Iceland	Cross-sectional	60	Elderly patients >65 years	37	83 (±8)	According to Ramel et al [28]	No MN: 41.7% (n=25) MN: 58.3% (n=35)	25(OH)D (nmol/L) Def: <25 (n=7) Ins: 25-75 (n=43) Suf: ≥75 (n=10)	No MN vs MN: 46.4 (± 21.5) vs 53.9 (±23.0) (p=0.22)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Soysal et al [29]	Turkey	Cross-sectional	615	Elderly patients ≥60 years	39	73 (±9)	No MN: MNA-SF 12-14 Risk of MN: MNA-SF 8-11 MN: MNA-SF 0-7	No MN: 33.7% (n=207) Risk of MN: 43.7% (n=269) MN: 22.6% (n=139)	Glu (mg/dL), TSH (uIU/mL), fT3 (nmol/L), fT4 (nmol/L), Creat (mg/dL), VitB12 (pmol/L), FA (ng/mL)	No MN vs risk of MN vs MN: Glu: 132.9 (±70.9) vs 145.7 (±80.2) vs 139.0 (±73.2) TSH: 3.6 (±15.6) vs 1.9 (±2.1) vs 2.2 (±3.7) fT3[a,d]: 3.6 (±0.9) vs 3.3 (±0.9) vs 2.9 (±1.0) fT4[c]: 14.5 (±3.6) vs 15.3 (±3.3) vs 15.4 (±4.0) Creat[d]: 1.1 (±0.8) vs 1.3 (±1.5) vs 1.7 (±1.6) VitB12: 374.3 (±235.7) vs 348.1 (±184.2) vs 382.6 (±212.1) FA: 8.4 (±3.9) vs 8.2 (±4.2) vs 7.7 (±3.7) [a] Risk of MN vs MN: p<0.002 [b] Risk of MN vs MN: p<0.05 [c] No MN vs MN: p<0.05 [d] No MN vs MN: p<0.001 Pearson correlation with MNA-SF: VitB12: r=0.01 (p>0.05); FA: r=0.16 (p>0.05)
Tas Kilic et al [21]	Turkey	Cross-sectional	62	Patients with systemic sclerosis	10	50 (±13)	No MN: MUST 0 Medium risk of MN: MUST 1 High risk of MN: MUST ≥2	No MN: 74.2% (n=46) MN: 25.8% (n=16)	VitB12 (pg/mL) Suf: >300 (n=18) Def: ≤300 (n=44)	No MN vs MN: Suf: 77.8% (n=14) vs 22.2% (n=4); Def: 72.7% (n=32) vs 27.3% (n=12) (p>0.05)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Terlikowska et al[24]	Poland	Cross-sectional	136	Caucasian women surgically treated for ovarian cancer	0	53 (±21)	No MN: PG-SGA A Mild MN: PG-SGA B Severe MN: PG-SGA >8	No MN: 44.9% (n=61) Mild MN: 36.0% (n=49) Severe MN: 19.1% (n=26)	ATRa, 25(OH)D, ATR, Ax, Lu, Zx, βTCP, γTCP, βCx, αTCP, Ly, αCt, βCt, Q_{10} (μmol/L)	No MN vs mild MN vs severe MN: ATRa: 0.004 (±0.002) vs 0.005 (±0.001) vs 0.005 (±0.001) (p=0.93) 25(OH)D: 0.08 (±0.03) vs 0.06 (±0.03) vs 0.03 (±0.01) (p=0.01) ATR: 5.6 (±1.8) vs 3.2 (±1.0) vs 2.0 (±0.9) (p=0.02) Ax: 0.003 (±0.001) vs 0.003 (±0.001) vs 0.002 (±0.001) (p=0.96) Lu: 0.55 (0.22) vs 0.51 (±0.22) vs 0.47 (±0.25) (p=0.29) Zx: 0.05 (±0.02) vs 0.03 (±0.01) vs 0.04 (±0.02) (p=0.98) β+γTCP: 1.4 (±0.7) vs 1.4 (0.7) vs 1.3 (0.2) (p=0.93) βCx: 0.007 (±0.004) vs 0.006 (±0.003) vs 0.005 (±0.002) (p=0.97) αTCP: 21.9 (±7.1) vs 19.0 (±5.2) vs 17.6 (±4.5) (p=0.09) Ly: 0.13 (±0.09) vs 0.12 (±0.05) vs 0.11 (±0.09) (p=0.25) αCt: 0.06 (±0.05) vs 0.06 (±0.05) vs 0.05 (±0.05) (p=0.08) βCt: 0.25 (±0.08) vs 0.23 (±0.14) vs 0.23 (±0.18) (p=0.90) Q_{10}: 0.03 (±0.04) vs 0.03 (±0.03) vs 0.03 (±0.02) (p=0.82)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Tsagari et al [30]	Greece	Prospective cohort	101	Elderly patients ≥65 years with a hip fracture	19	Females: 81 (75-86) Males: 80 (75-89)	No MN: MNA >23.5 Risk of MN: MNA 17-23.5 MN: MNA <17	Mean (±SD) MNA score: Females: 20 (18-22) Males: 21 (15-24)	25(OH)D (ng/mL) Ins: <20 Suf: ≥20	Pearson correlation with MNA: Total: r=0.41 (p<0.001), females: r=0.33 (p<0.001), males: r=0.56 (p=0.007) Discriminatory performance of MNA to predict Ins 25(OH)D: *Total population:* AUC 0.84 [SE 0.06, 95% CI 0.72-0.96] (p=0.01). MNA <25.75: Sensitivity 90.7% and specificity 77.8% *Only females:* AUC 0.85 [SE 0.08, 95% CI 0.70-1.00] (p=0.009) MNA <24: Sensitivity 92.1% and specificity 60%
Venzin et al [41]	Switzerland	Prospective cohort	430 (423 are included in NA)	Patients admitted to the internal medicine department, without patients directly admitted to the ICU	52	63 (±19)	No MN: MNA >23.5 Risk of MN: MNA 17-23.5 MN: MNA <17	No MN: 69.5% (n=294) Risk of MN: 20.1% (n=85) MN: 10.4% (n=44)	BUN (mmol/L), Creat (μmol/L)	No MN vs risk of MN vs MN: BUN: 7.4 (±5.2) vs 8.0 (±6.9) vs 9.5 (±9.6) (p>0.05) Creat: 89.2 (±79.6) vs 102.8 (±111.9) vs 94.5 (±72.8) (p>0.05)
Vischer et al [31]	Switzerland	Cross-sectional	164 (163 are included in NA)	Patients receiving geriatric inpatient care	30	85 (±6)	No MN: MNA-SF 12-14 Risk of MN: MNA-SF 8-11 MN: MNA-SF 0-7	No MN: 31.9% (n=52) Risk of MN: 50.3% (n=82) MN: 17.8% (n=29)	Iron (μmol/L), 25(OH)D (nmol/L)	No MN vs risk of MN vs MN: Iron: 10.8 (±4.9) vs 11.3 (±7.3) vs 9.7 (±5.1) (p>0.05) 25(OH)D: 40.4 (±22.4) vs 43.7 (±23.3) vs 46.6 (±39.3) (p>0.05)

Table 1 *(Continued)*

Reference	Country	Design	n	Hospitalized population	Male (%)	Age (yrs)*	Nutritional assessment	Prevalence MN	Biomarker(s)	Relation between biomarker(s) and nutritional status*
Vosoughi et al [23]	Iran	Prospective cohort	185	Patients admitted to the ICU	51	56 (±1)	No MN: MAMC >90; Mild MN: MAMC 81-90; Moderate MN: MAMC 70-80; Severe MN: MAMC <70	No MN: 61% (n=113); Mild MN: 29% (n=54); Moderate-severe MN: 10% (n=18)	25(OH)D (ng/mL) Ins: < 30 Suf: 30-100	No MN vs mild MN vs moderate-severe MN: Ins: 61% (n=105) vs 29% (n=50) vs 10% (n=18); Suf: 67% (n=8) vs 33% (n=4) vs 0% (n=0); (p=0.5) Ins: no MN: OR=1***; mild MN: OR=0.99 (95% CI 0.96-1.04; p=0.89)***; moderate-severe MN: OR=0.89 (95% CI 0.77-1.04; p=0.14)***

5th P, 5th percentile of the National Health and Nutrition Examination Survey standardized for age and sex; ALC, Absolute lymphocyte count (x109 cells/L); Allo-HSCT, allogeneic hematopoietic stem cell transplantation; AUC, Area under the curve; BMI, Body Mass Index (kg/m2); BW, Body weight (kg); CHF, Congestive heart failure; CI, Confidence interval; Def, Deficiency; ICU, Intensive care unit; Ins, Insufficiency; MAC, Mid-arm circumference (cm); MAMC, Mid-arm muscle circumference, calculated through Mid-arm circumference (cm) – 3/14 x TSF (%); MN, Malnutrition/Malnourished; MNA-SF, Mini Nutritional Assessment-Short Form; MUST, Malnutrition Universal Screening Tool; NA, Nutritional assessment; NRS-2002, Nutritional Risk Screening 2002; NYHA, New York heart association; OR, Odds Ratio; PG-SGA, Patient-Generated Subjective Global Assessment; SA, Serum albumin (g/dL); SE, Standard error; SevDef, Severe deficiency; SGA, Subjective Global Assessment; SIRS, Systemic inflammatory response syndrome; SPA, Serum prealbumin (mg/dL); Suf, sufficiency; TSF, Skin-fold thickness at triceps (cm); uWL, Unintentional weight loss; WN, Well-nourished; Yrs, Years %ucOC, Percentage of osteocalcin that is not carboxylated; 1,25di(OH)D, 1,25-dihydroxycholecalciferol (pmol/L); 25(OH)D, 25-hydroxycholecalciferol (ng/mL, nmol/L or µmol/L); 3-UPA, 3-Ureidopropionate; Andros-S, Andro steroid monosulfate 2; ATR, All-trans-retinol (µmol/L); ATRa, All-trans-retinoic acid (µmol/L); Ax, Astaxanthin (µmol/L); BUN, Blood urea nitrogen (mmol/L); Ca, Calcium (mmol/L); CI, Chiro-inositol; Creat, Creatinine (mg/dL); Ct, Carotenoids (µg/dL); CysC, Cystatin C (mg/L); EGRAC, erythrocyte glutathione reductase activation coefficient; FA, Folic acid (ng/mL or nmol/L); fT3, Free T3 (nmol/L); fT4, Free T4 (nmol/L); γ-GPA, γ-Glutamylphenylalanine; Glu, Glucose (mg/dL); HC, Homocysteine (µmol/L); Hx, Hypoxanthine; Iron, Serum iron (µmol/L); Kyn, Kynurenine; Lu, Luthein (µmol/L); Ly, Lycopene (µmol/L); MTA, 5-Methylthioadenosine; NAM, N-acetylmethionine; NAPhe, N-acetylphenylalanine; OC, Osteocalcin (ng/mL); OH-PA, 4-hydroxyphenylacetate; OH-PL, 3-(4-hydroxyphenyl)lactate; P-GPA, 1-Palmitoylglycerophosphoethanolamine; PIVKA-II, Protein Induced Vitamin K Absence or Antagonist-II; PL, Phenyllactate; PTH, Parathyroid hormone (pg/mL); PyrGln, Pyroglutamine; Q10, Coenzyme Q10 (µmol/L); S-GPA, 1-stearoylglycerophosphoethanoamine; TMAO, Trimethylamine-N-oxide (µmol/L); TML, N-6-trimethyllysine; TrpB, Tryptophan betaine; TSH, thyroid stimulating hormone (uIU/mL); Val, Valerate; VitA, Vitamin A (µg/dL); VitB1, Vitamin B1 (thiamin) (ng/mL); VitB3, Vitamin B3 (nicotinamide); VitB12, Vitamin B12 (pg/mL or pmol/L); VitC, Vitamin C/Ascorbic acid (mg/dL); VitE, Vitamin E (µg/dL); VitK1, Vitamin K1/Phylloquinone (nmol/L); Zx, Zeaxanthin (µmol/L); αCt, α-carotene (µmol/L); αTCP, α-Tocopherol (µmol/L); βCt, β-Carotene (µmol/L); βCx, β-cryptoxanthin (µmol/L); βTCP, β-Tocopherol (µmol/L); γTCP, γ-Tocopherol (µmol/L)

*Data presented as Mean (±SD), Median [IQR], Median (range), or Percentage (number)

** Adjusted for tumor type, BMI category, race, and gender

*** Adjusted for age, sex, length of hospital stay, infection, C-reactive protein

Table 2: Risk of Bias in the included cohort studies according to MINORS criteria

	Avelino et al [39]	Christopher et al [32]	Chou et al [19]	Cunha et al [26]	Djurasinovic et al [33]	Førli et al [36]
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	1	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. Endpoints appropriate to aim of study	2	2	2	2	2	2
5. Unbiased assessment of study endpoints	0	0	0	0	0	0
6. Follow-up period appropriate to aim of study	2	2	2	2	2	2
7. <5% lost to follow-up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	2	0	0	0
9. An adequate control group	2	2	2	1	2	1
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	1	1	2	1	1	1
12. Adequate statistical analyses	2	2	2	2	2	2
Total	19	19	22	17	19	18
	Holden et al [37]	Hosseini et al [27]	Jatoi et al [40]	Katić et al [20]	Li et al [35]	Mogensen et al [34]
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	2	2	2	2	2	2
4. Endpoints appropriate to aim of study	2	2	2	2	2	2
5. Unbiased assessment of study endpoints	0	0	0	0	0	0
6. Follow-up period appropriate to aim of study	2	2	2	2	2	2
7. <5% lost to follow-up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	0	0	0	0
9. An adequate control group	2	2	1	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	0	1	0	2	1	1
12. Adequate statistical analyses	2	2	1	2	2	2
Total	18	19	16	20	19	19
	Olivera-Soto et al [38]	Pourhassan et al [25]	Ramel et al [28]	Ramel et al [22]	Soysal et al [29]	Tas Kilic et al [21]
1. Clearly stated aim	2	2	2	2	2	2
2. Inclusion of consecutive patients	2	2	2	2	2	2
3. Prospective collection of data	2	0	2	2	2	2
4. Endpoints appropriate to aim of study	2	2	2	2	2	2
5. Unbiased assessment of study endpoints	0	0	0	0	0	0
6. Follow-up period appropriate to aim of study	2	2	2	2	2	2
7. <5% lost to follow-up	2	2	2	2	2	2
8. Prospective calculation of study size	0	0	0	2	0	0
9. An adequate control group	2	2	2	2	2	2
10. Contemporary groups	2	2	2	2	2	2
11. Baseline equivalence of groups	1	1	0	0	1	2

Table 2 *(Continued)*

	Olivera-Soto et al [38]	Pourhassan et al [25]	Ramel et al [28]	Ramel et al [22]	Soysal et al [29]	Tas Kilic et al [21]
12. Adequate statistical analyses	2	2	2	2	2	2
Total	19	17	18	20	19	20
	Terlikowska et al [24]	Tsagari et al [30]	Venzin et al [41]	Vischer et al [31]	Vosoughi et al [23]	
1. Clearly stated aim	2	2	1	2	2	
2. Inclusion of consecutive patients	2	2	2	2	2	
3. Prospective collection of data	0	2	2	2	2	
4. Endpoints appropriate to aim of study	2	2	2	2	2	
5. Unbiased assessment of study endpoints	0	0	0	0	0	
6. Follow-up period appropriate to aim of study	2	2	2	2	2	
7. <5% lost to follow-up	2	2	2	2	2	
8. Prospective calculation of study size	0	0	0	0	2	
9. An adequate control group	2	2	2	2	2	
10. Contemporary groups	2	2	2	2	2	
11. Baseline equivalence of groups	0	1	1	1	2	
12. Adequate statistical analyses	2	2	2	2	2	
Total	16	19	18	19	22	

Criteria were scored 2 (reported and adequate), 1 (reported but inadequate) or 0 (not reported), with a maximum total score of 24

Patient Population

The selected studies included 3,803 hospitalized patients, both ICU patients (n=365) and non-ICU patients (n=3,438) (**Table 1**). Eight studies focused on elderly patients older than 60 or 65 years old,[22,25-31] and the other studies included all adult patients. Regarding the reason for hospital admission, three studies focused on patients with malignancies,[24,32,33] one on patients with chronic graft-vs-host disease after allogeneic hematopoietic stem cell transplantation,[20] two studies included patients with SIRS or sepsis[19,34] and two studies included patients with fractures.[30,35] Other studied patient groups included patients with pulmonary disease considered for lung transplantation,[36] chronic kidney disease,[37,38] chronic heart failure,[27] and systemic sclerosis.[21] The other articles included all patients admitted to the hospital ward or ICU.[22,23,25,26,28,29,31,39-41]

Prevalence of Malnutrition

In five studies including only elderly patients, 44-81% were at risk of malnutrition and 10-39% were diagnosed with malnutrition based on the MNA or MNA Short-Form (MNA-SF).[25,27,29-31] In three other studies, 16.5% of the elderly patients had a BMI below 18.5 kg/m^2 and 58% were diagnosed with malnutrition based on a

combination of anthropometric measurements and laboratory values.[22,26,28] In three studies with patients with (hematologic) malignancies, 28-36% were diagnosed with mild malnutrition, and 6-24% had severe malnutrition based on the PG-SGA.[20,24,32] Djurasinovic et al[33] used the Nutritional Risk Screening (NRS-2002) and found that 45% of the patients with lymphoproliferative malignancies were malnourished. In the other patient groups, 20-26% of the patients were mildly malnourished and 0-24% were severely malnourished based on the SGA.[37-39] In the study by Venzin et al,[41] 20% were at risk of malnutrition and 10% were malnourished according to the MNA. Vosoughi et al[23] found that 29% of the patients admitted to the ICU were mildly malnourished and 10% were severely malnourished based on the mid-arm muscle circumference (MAMC). Other nutritional assessment tools found a prevalence of malnutrition between 26% and 74%.[19,21,34-36,40]

Metabolites and Malnutrition

Many different plasma metabolites were studied in their relation with malnutrition. No association was found between creatinine levels and the SGA or MNA score,[39,41] but creatinine levels were significantly higher in the patients with malnutrition diagnosed with the MNA-SF (1.7 (±1.6) mg/dL vs 1.1 (±0.8) mg/dL ($p<0.001$)).[29] The NRS-2002 score was found to be significantly lower in the group with high Trimethylamine N-oxide (TMAO) levels, compared to the groups with median or low TMAO levels (NRS-2002 score 4.0 (3.0-4.0) vs 4.0 (4.0-5.8) vs 5.0 (5.0-6.0) ($p<0.001$)).[19] The percentage of osteocalcin that is not carboxylated (%ucOC) was not found to be related to the SGA score ($r=0.02$; $p=0.79$).[37] Osteocalcin levels were significantly higher in the well-nourished patients compared to the patients with malnutrition based on the NRS-2002 score (3.7 (±0.5) vs 1.3 (±0.2) ng/mL; $p=0.00$).[35] Hosseini et al[27] and Venzin et al[41] did not find a relation between blood urea nitrogen (BUN) levels and malnutrition diagnosed with the MNA score ($p=0.9$ and $p>0.05$ resp.), but Mogensen et al[34] found that high urea levels might be predictive for malnutrition when diagnosed through a combination of anthropometric measurements and laboratory results (VIP=2.05). The other metabolites that were the best predictors of malnutrition in a partial least squares discriminant analysis, are described in **Table 1**. Mogensen et al[34] also found that the levels of 5-methylthioadenosine, N-6-trimethyllysine, N-acetylmethionine, pyroglutamine, hypoxanthine, kynurenine, and phenyllactate were significantly higher, and the levels of 1-palmitoylglycerophosphoethanolamine, and valerate were significantly lower in patients with malnutrition compared to the well-nourished patients ($p<0.05$). Ramel et al[28]

concluded that cystatine C levels were significantly higher in the patients with malnutrition diagnosed through a combination of anthropometric measurements and laboratory results. Free T3 levels were significantly lower (2.9 (±1.0) nmol/L vs 3.6 (±0.9) nmol/L) and free T4 levels were significantly higher (15.4 (±4.0) nmol/L vs 14.5 (±3.6) nmol/L) in the patients with malnutrition based on the MNA-SF compared to the patients without malnutrition.[29,31]

Vitamins and Malnutrition

25(OH)D levels seemed to be lower in patients with malnutrition diagnosed with the PG-SGA score compared to the well-nourished patients.[20,24] However, when adjusted for tumor type, BMI category, race, and gender, 25(OH)D levels were not related to the PG-SGA score.[32] Additionally, malnutrition diagnosed with the NRS-2002 was associated with a higher prevalence of severe 25(OH)D deficiency and with lower 25(OH)D levels.[33,35] Malnutrition based on the MNA score was also found to be related with lower 25(OH)D levels ($p<0.001$).[30] On the other hand, the MNA-SF, SGA, BMI, MAMC, and a combination of anthropometric measurements and laboratory results were not related to 25(OH)D levels ($p>0.05$).[31,36-38] 1,25-dihydroxycholecalciferol (1,25di(OH)D) was not related to a BMI <20 kg/m^2.[36]

Vitamin C levels were significantly lower in the severely and mildly malnourished group compared to the well-nourished group based on the SGA score (0.3 (0.0-0.9) mg/dL vs 0.5 (0.2-1.3) mg/dL vs 0.7 (0.1-1.5) mg/dL ($p<0.05$)).[39] Vitamin C deficiency was also more common in the group with malnutrition based on the SGA score and a BMI <18.5 kg/m^2.[26,39] A BMI <18.5 kg/m^2 was also related to a higher rate of carotenoids deficiency, but not related to a vitamin A, vitamin E, or vitamin B2 deficiency (diagnosed with the erythrocyte glutathione reductase activation coefficient (EGRAC)).[26] Vitamin K1 and the related Protein Induced Vitamin K Absence or Antagonist-II (PIVKA-II) were not related to malnutrition diagnosed with the SGA or a combination of anthropometric measurements and laboratory results.[37,40] The presence of vitamin B12 deficiency was not significantly different in the malnourished group based on the MUST score and vitamin B12 levels were not significantly different in the groups based on the MNA-SF or a combination of anthropometric measurements and laboratory results.[21,28,29] Vitamin B1 (thiamin) was not related to malnutrition measured using the MNA-SF, and vitamin B9 (folic acid) was not related to a combination of anthropometric measurements and laboratory results or the MNA-SF.[25,28,29] Nicotinamide (vitamin

B3) levels were significantly lower in patients with malnutrition compared to the well-nourished patients ($p<0.05$).[34] Terlikowska et al[24] studied many carotenoids and tocopherols in the relation with the PG-SGA score. Only all-trans-retinol levels were significantly lower in the severely malnourished group compared to the mildly malnourished and the well-nourished group (2.0 (±0.9) µmol/L vs 3.2 (±1.0) µmol/L vs 5.6 (±1.8) µmol/L ($p=0.02$)).

DISCUSSION

To our knowledge, this is the first systematic review that summarizes the evidence about the value of plasma metabolites and vitamins for assessing nutritional status of hospitalized patients. Our review demonstrates that several metabolites and vitamins are related to malnutrition and may offer a promising method for assessment of nutritional status in hospitalized patients.

Most of the metabolites that showed significant difference between the malnourished and well-nourished hospitalized patients are shown in **Figure 2**.[19,26,29,34,35,39,42-55] This figure depicts the relationship between these metabolites (striped and black boxes) and other metabolic pathways in the body. The essential amino acids lysine, methionine, phenylalanine, and tryptophan play an important role within the pathways in **Figure 2**. N-6-trimethyllysine, 5-methylthioadenosine, hypoxanthine, and N-acetylmethionine are all related to the methionine cycle,[12,56-59] and the levels of these metabolites were all found to be increased in patients with malnutrition.[34] Phenyllactate, 4-hydroxyphenylacetate, 3-(4-hydroxyphenyl)lactate, N-acetylphenylalanine, and pyroglutamine are all related to the phenylalanine and/or glutamate metabolism.[12,60-62] All 5 metabolite levels were increased in patients with malnutrition.[34] Andro steroid monosulfate 2, 1-palmitoylglycerophosphoethanolamine, and 1-stearoylglycerophosphoethanolamine are involved in the lipid metabolism, and these levels were all decreased in patients with malnutrition. Chiro-inositol is also related to the lipid metabolism, but the level of this metabolite was increased in patients with malnutrition.[12,34]

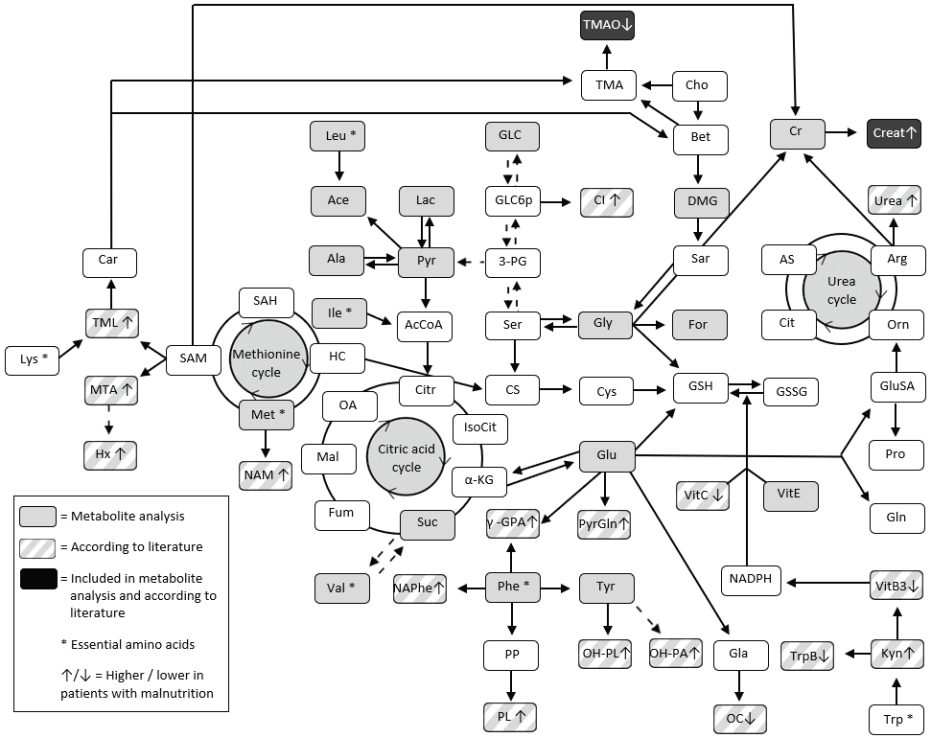

Figure 2: Metabolites analyzed in this study within their metabolic cycles and their association with malnutrition according to available literature

3-PG, 3-phosphoglycerate; AcCoA, Acetyl-CoA; Ace, Acetic acid; Ala, Alanine; Arg, Arginine; AS, Argininosuccinate; α-KG, α-ketoglutarate; Bet, Betaine; Car, Carnitine; Cho, Choline; CI, Chiro-inositol; Cit, Citrulline; Citr, Citrate; Cr, Creatine; Creat, Creatinine; CS, Cystathionine; Cys, Cysteine; DMG, N,N-Dimethylglycine; For, Formic acid; Fum, Fumarate; Gla, γ-carboxyglutamic acid; GLC, glucose; GLC6p, Glucose-6-phosphate; Gln, Glutamine; Glu, Glutamic acid; GluSA, Glutamate-1-semialdehyde; Gly, Glycine; GSH, Reduced glutathione; GSSG, Glutathione disulfide; γ-GPA, γ-Glutamyl phenylalanine; HC, Homocysteine; Hx, Hypoxanthine; Ile, Isoleucine; IsoCit, Isocitrate; Kyn, Kynurenine; Lac, Lactic acid; Leu, Leucine; Lys, Lysine; Mal, Malate; Met, Methionine; MTA, 5-Methylthioadenosine; NADPH, Nicotinamide-adenine-dinucleotidephosphate; NAM, N-acetylmethionine; NAPhe, N-acetylphenylalanine; OA, Oxaloacetate; OC, Osteocalcin; OH-PA, 4-hydroxyphenylacetate; OH-PL, 3-(4-hydroxyphenyl)lactate; Orn, Ornithine; Phe, Phenylalanine; PL, Phenyllactate; PP, Phenylpyruvate; Pro, Proline; Pyr, Pyruvic acid; PyrGlu, Pyroglutamate; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; Sar, Sarcosine; Ser, Serine; Suc, Succinic acid; TMA, Trimethylamine; TMAO, Trimethylamine-N-oxide; TML, N-6-trimethyllysine; Trp, Tryptophan; TrpB, Tryptophan Betaine; Tyr, Tyrosine; Val, Valine; VitB3, Vitamin B3 (nicotinamide); VitC, Vitamin C; VitE, Vitamin E;

Kynurenine is responsible for 95% of the catabolic route of tryptophan and results in the production of tryptophan betaine and nicotinamide (vitamin B3).[63-65] Nicotinamide is the precursor of nicotinamide-adenine-dinucleotidephosphate (NADPH),[66] which is, together with vitamin E and vitamin C, responsible for the conversion of glutathione disulfide to reduced glutathione.[67-70] According to Mogensen et al[34] kynurenine levels were higher in patients with malnutrition, and tryptophan betaine and nicotinamide levels were lower in patients with malnutrition. The percentage of vitamin C deficiency was significantly higher in the group with malnutrition according to Avelino et al[39] and Cunha et al.[26] Clinical studies have shown a correlation between elevated TMAO levels and an increased risk for cardiovascular events.[71] Interestingly, Chou et al[19] stated that decreased TMAO levels might be indicative of malnutrition.

Vitamins can be classified as fat-soluble or water-soluble. Vitamin A, D, E, and K are considered to be fat-soluble vitamins and are absorbed and transported similarly. Fat-soluble vitamins are packed into newly formed micelles in the small intestine and absorbed into the enterocytes. The vitamins are then repackaged into chylomicrons and secreted into the lymphatic system and the bloodstream.[72] After release of the fat-soluble vitamins, retinol-binding proteins, vitamin D binding proteins, and α-tocopherol transporting proteins transport vitamin A, D, and E, respectively, through the body.[73,74] Fat and protein are thus necessary for absorption of fat-soluble vitamins into the body and transport through the body. Several studies have found a relationship between low albumin levels and vitamin A, D, and E deficiencies in hospitalized patients.[73,75-77] Malnourished patients might therefore not only have a lower vitamin intake but the absorption and transport of vitamins might also be diminished, which can cause a further decrease in vitamin levels. On the other hand, most of the vitamins D and E in the body are stored in fat tissue.[78,79] When patients become acutely malnourished, stored vitamins might be released into the bloodstream when fat is metabolized to produce adenosine triphosphate. Differentiating between chronic malnutrition (concerning patients who are already malnourished upon admission) and acute malnutrition (concerning patients who become malnourished during hospital admission) might therefore be important when using vitamins for nutritional assessment.

Metabolites may also be used as prognostic biomarkers to assess the risk of developing complications during admission.[80] Mogensen et al[34] and Rogers et

al[81] studied the relationship between several metabolites and 28-day mortality. 3-(4-hydroxyphenyl)lactate, gamma-glutamylphenylalanine, and kynurenine were studied by both researchers and they found a significant relation between these metabolites and mortality in critically ill patients (P<0.05). In total, Rogers et al[81] found 57 metabolites to be related to the 28-day mortality.

Limitations

The most important limitation of this systematic review is that the researchers of the included studies used different nutritional assessment tools. This illustrates the fact that a criterion standard for the assessment of nutritional status is lacking, which poses a major challenge in nutritional research. Another limitation is that hospitalized patients with very diverse underlying conditions were included. Despite these limitations, our study is important because it points out the possibilities for future research.

Recommendations for further research

Based upon the findings of this systematic review, metabolites and vitamins offer a promising method for assessing the nutritional status in hospitalized patients. However, many challenges and questions need to be addressed. Further studies involving nutrition-related research in hospitalized patients should incorporate the following recommendations. First, the metabolite and vitamin levels should be assessed in large patient groups to obtain statistical power and identify clinically relevant metabolites. Second, standardized data collection, preferably by registered dietitians, on clinically relevant time points and universal assessment tools should be used to make international research comparable. Third, metabolite and vitamin levels should be measured at different time points during admission to analyze fluctuations over time. Our study group has initiated a multicenter prospective cohort study to gain greater insight in the value of lipoproteins and small metabolites for the assessment of nutritional status in severely injured patients.[82] There is a need for an objective marker to assess nutritional status in this patient group, as nutritional assessment in these patients is even more difficult than in the standard hospitalized patients. The goal of our study is to analyze the metabolite profiles of severely injured patients (Injury Severity Score ≥16) during their ICU stay, including several of the biomarker candidates described in this review.

CONCLUSION

The evidence for metabolites and vitamins as predictors of nutritional status is scarce; however, according to this literature review several metabolites partaking in the methionine, purine, glutathione, carnitine, phenylalanine, and tryptophan pathways, as well as a number of vitamins seem to be associated with malnutrition in hospitalized patients. More research is needed to further evaluate the value of metabolites and vitamins to diagnose malnutrition and assess the risk of developing malnutrition in hospitalized patients. The clinical usability and effectiveness of the metabolite analysis should be investigated for use in clinical practice.

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APPENDIX 1

PubMed search

((("Metabolomics"[majr] OR "Metabolomics"[ti] OR "metabolites"[ti] OR "metabolite"[ti] OR "Metabolomic"[ti] OR "Metabolome"[majr] OR "Metabolome"[ti] OR "Metabolom*"[ti] OR "Metabolic Profile"[ti] OR "Metabolic Profiles"[ti] OR "Metabolic changes"[ti] OR "Metabolic change"[ti] OR ("Malnutrition/metabolism"[majr] AND "metabolism"[Subheading:NoExp] AND "analysis"[Subheading:noexp])) AND ("Nutritional status"[majr] OR "Nutritional status"[ti] OR "Nutrition status"[ti] OR "Malnutrition"[majr] OR "Malnutrition"[ti] OR "Nutritional Deficiency"[ti] OR "Nutritional Deficiencies"[ti] OR "Undernutrition"[ti] OR "Malnourishment"[ti] OR "Malnourish*"[ti] OR "Ascorbic Acid Deficiency"[ti] OR "Ascorbic Acid Deficient"[ti] OR "Avitaminosis"[ti] OR "Beri beri"[ti] OR "Beriberi"[ti] OR "Choline Deficiency"[ti] OR "Choline Deficient"[ti] OR "Chronic Kidney Disease-Mineral and Bone Disorder"[ti] OR "Deficiency Disease"[ti] OR "Deficiency Diseases"[ti] OR "Folic Acid Deficiency"[ti] OR "Folic Acid Deficient"[ti] OR "Hyperhomocysteinaemia"[ti] OR "Hyperhomocysteinemia"[ti] OR "Hyperhomocysteinemia"[ti] OR "Kwashiorkor"[ti] OR "Magnesium Deficiency"[ti] OR "Magnesium Deficient"[ti] OR "Osteomalacia"[ti] OR "Pellagra"[ti] OR "Pernicious Anaemia "[ti] OR "Pernicious Anemia "[ti] OR "Potassium Deficiency"[ti] OR "Potassium Deficient"[ti] OR "Protein Deficiency"[ti] OR "Protein Deficient"[ti] OR "Refeeding Syndrome"[ti] OR "Riboflavin Deficiency"[ti] OR "Riboflavin Deficient"[ti] OR "Rickets"[ti] OR "Scurvy"[ti] OR "Severe Acute Malnutrition"[ti] OR "Starvation"[ti] OR "Steatitis"[ti] OR "Subacute Combined Degeneration"[ti] OR "Swayback"[ti] OR "Thiamine Deficiency"[ti] OR "Thiamine Deficient"[ti] OR "Vitamin A Deficiency"[ti] OR "Vitamin A Deficient"[ti] OR "Vitamin B 12 Deficiency"[ti] OR "Vitamin B 12 Deficient"[ti] OR "Vitamin B 6 Deficiency"[ti] OR "Vitamin B 6 Deficient"[ti] OR "Vitamin B Deficiency"[ti] OR "Vitamin B Deficient"[ti] OR "Vitamin D Deficiency"[ti] OR "Vitamin D Deficient"[ti] OR "Vitamin E Deficiency"[ti] OR "Vitamin E Deficient"[ti] OR "Vitamin K Deficiency"[ti] OR "Vitamin K Deficiency Bleeding"[ti] OR "Vitamin K Deficient"[ti] OR "Wernicke Encephalopathy"[ti]) NOT (("Animals"[mesh] OR "veterinary"[ti] OR "rabbit"[ti] OR "rabbits"[ti] OR "animal"[ti] OR "animals"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rodent"[ti] OR "rodents"[ti] OR "rat"[ti] OR "rats"[ti] OR "pig"[ti] OR "pigs"[ti] OR "porcine"[ti] OR "horse"[ti] OR "horses"[ti] OR "equine"[ti] OR "cow"[ti] OR "cows"[ti] OR "bovine"[ti] OR "goat"[ti] OR "goats"[ti] OR "sheep"[ti] OR "ovine"[ti] OR "canine"[ti] OR "dog"[ti] OR "dogs"[ti] OR "feline"[ti] OR "cat"[ti] OR "cats"[ti]) NOT

"Humans"[mesh]) AND ("Patients"[mesh] OR "hospitalized"[tw] OR "hospitalised"[tw] OR "patients"[tw] OR "patient"[tw] OR "Patient Care"[mesh] OR "Hospital Units"[mesh] OR "Hospitals"[mesh])) **OR** (("Malnutrition"[mesh] OR "Malnutrition"[tw] OR "Nutritional Deficiency"[tw] OR "Nutritional Deficiencies"[tw] OR "Undernutrition"[tw] OR "Malnourishment"[tw] OR "Malnourish*"[tw] OR "Ascorbic Acid Deficiency"[tw] OR "Ascorbic Acid Deficient"[tw] OR "Avitaminosis"[tw] OR "Beri beri"[tw] OR "Beriberi"[tw] OR "Choline Deficiency"[tw] OR "Choline Deficient"[tw] OR "Chronic Kidney Disease-Mineral and Bone Disorder"[tw] OR "Deficiency Disease"[tw] OR "Deficiency Diseases"[tw] OR "Fetal Nutrition Disorders"[tw] OR "Folic Acid Deficiency"[tw] OR "Folic Acid Deficient"[tw] OR "Hyperhomocysteinaemia"[tw] OR "Hyperhomocysteinemia"[tw] OR "Hyperhomocysteinemia"[tw] OR "Kwashiorkor"[tw] OR "Magnesium Deficiency"[tw] OR "Magnesium Deficient"[tw] OR "Osteomalacia"[tw] OR "Pellagra"[tw] OR "Pernicious Anaemia "[tw] OR "Pernicious Anemia "[tw] OR "Potassium Deficiency"[tw] OR "Potassium Deficient"[tw] OR "Protein Deficiency"[tw] OR "Protein Deficient"[tw] OR "Refeeding Syndrome"[tw] OR "Riboflavin Deficiency"[tw] OR "Riboflavin Deficient"[tw] OR "Rickets"[tw] OR "Scurvy"[tw] OR "Severe Acute Malnutrition"[tw] OR "Starvation"[tw] OR "Steatitis"[tw] OR "Subacute Combined Degeneration"[tw] OR "Swayback"[tw] OR "Thiamine Deficiency"[tw] OR "Thiamine Deficient"[tw] OR "Vitamin A Deficiency"[tw] OR "Vitamin A Deficient"[tw] OR "Vitamin B 12 Deficiency"[tw] OR "Vitamin B 12 Deficient"[tw] OR "Vitamin B 6 Deficiency"[tw] OR "Vitamin B 6 Deficient"[tw] OR "Vitamin B Deficiency"[tw] OR "Vitamin B Deficient"[tw] OR "Vitamin D Deficiency"[tw] OR "Vitamin D Deficient"[tw] OR "Vitamin E Deficiency"[tw] OR "Vitamin E Deficient"[tw] OR "Vitamin K Deficiency"[tw] OR "Vitamin K Deficiency Bleeding"[tw] OR "Vitamin K Deficient"[tw] OR "Wernicke Encephalopathy"[tw]) AND ("Nutritional status"[mesh] OR "Nutritional status"[tw] OR "Nutrition status"[tw] OR "Nutrition Assessment"[mesh] OR "Nutrition Assessment"[tw] OR "Nutritional Assessment"[tw]) AND ("Vitamins"[majr] OR "Vitamins"[ti] OR "Vitamin"[ti] OR "Vitamin A"[ti] OR "Vitamin B 12"[ti] OR "Vitamin B 6"[ti] OR "Vitamin D"[ti] OR "Vitamin E"[ti] OR "Vitamin K"[ti] OR "Vitamin K 1"[ti] OR "Vitamin K 2"[ti] OR "Vitamin K 3"[ti] OR "Vitamin U"[ti] OR "1 alpha-hydroxyergocalciferol"[Supplementary Concept] OR "24,25-Dihydroxyvitamin D 3"[majr] OR "25-Hydroxyvitamin D 2"[majr] OR "7-dehydrocholesterol"[Supplementary Concept] OR "Acetylcarnitine"[majr] OR "alpha-cryptoxanthin"[Supplementary Concept] OR "alpha-Tocopherol"[majr] OR "aminopyrine, dexamethasone, phenylbutazone, thiamine, vitamin B12 drug combination"[Supplementary Concept] OR

"Ascorbic Acid"[majr] OR "beta Carotene"[majr] OR "Beta-Cryptoxanthin"[majr] OR "beta-Tocopherol"[majr] OR "Biotin"[majr] OR "Calcifediol"[majr] OR "Calcitriol"[majr] OR "calcium ascorbate"[Supplementary Concept] OR "Cholecalciferol"[majr] OR "choline, dehydrocholic acid, magnesium orotate, orotic acid, Vitamin B12 drug combination"[Supplementary Concept] OR "Cobamides"[majr] OR "Cod Liver Oil"[majr] OR "coenzyme Q10"[Supplementary Concept] OR "Dehydroascorbic Acid"[majr] OR "Dehydrocholesterols"[majr] OR "Dihydrotachysterol"[majr] OR "Dihydroxycholecalciferols"[majr] OR "Ergocalciferols"[majr] OR "Ergosterol"[majr] OR "Flavin Mononucleotide"[majr] OR "Folic Acid"[majr] OR "Formyltetrahydrofolates"[majr] OR "Fursultiamin"[majr] OR "gamma-Tocopherol"[majr] OR "Hydroxocobalamin"[majr] OR "Hydroxycholecalciferols"[majr] OR "Inositol"[majr] OR "Leucovorin"[majr] OR "Niacin"[majr] OR "Niacinamide"[majr] OR "Nicorandil"[majr] OR "Nicotinic Acids"[majr] OR "Palmitoylcarnitine"[majr] OR "Pantothenic Acid"[majr] OR "provitamin C"[Supplementary Concept] OR "Pteroylpolyglutamic Acids"[majr] OR "Pyridoxal"[majr] OR "Pyridoxal Phosphate"[majr] OR "Pyridoxamine"[majr] OR "Pyridoxine"[majr] OR "Riboflavin"[majr] OR "sapotexanthin"[Supplementary Concept] OR "Tetrahydrofolates"[majr] OR "Thiamine"[majr] OR "Thiamine Monophosphate"[majr] OR "Thiamine Pyrophosphate"[majr] OR "Thiamine Triphosphate"[majr] OR "Thioctic Acid"[majr] OR "Tocopherols"[majr] OR "Tocotrienols"[majr] OR "Tocovid"[Supplementary Concept] OR "Vitamin A"[majr] OR "vitamin A, pentifyllin, nicotinic acid, and vitamin E combination"[Supplementary Concept] OR "Vitamin B 12"[majr] OR "Vitamin B 6"[majr] OR "Vitamin D"[majr] OR "Vitamin E"[majr] OR "Vitamin K"[majr] OR "Vitamin K 1"[majr] OR "Vitamin K 2"[majr] OR "Vitamin K 3"[majr] OR "Vitamin U"[majr] OR "Antioxidants"[majr] OR "Antioxidant"[ti] OR "Antioxidants"[ti]) NOT (("Animals"[mesh] OR "veterinary"[ti] OR "rabbit"[ti] OR "rabbits"[ti] OR "animal"[ti] OR "animals"[ti] OR "mouse"[ti] OR "mice"[ti] OR "rodent"[ti] OR "rodents"[ti] OR "rat"[ti] OR "rats"[ti] OR "pig"[ti] OR "pigs"[ti] OR "porcine"[ti] OR "horse"[ti] OR "horses"[ti] OR "equine"[ti] OR "cow"[ti] OR "cows"[ti] OR "bovine"[ti] OR "goat"[ti] OR "goats"[ti] OR "sheep"[ti] OR "ovine"[ti] OR "canine"[ti] OR "dog"[ti] OR "dogs"[ti] OR "feline"[ti] OR "cat"[ti] OR "cats"[ti]) NOT "Humans"[mesh]) AND ("Patients"[mesh] OR "hospitalized"[tw] OR "hospitalised"[tw] OR "patients"[tw] OR "patient"[tw] OR "Patient Care"[mesh] OR "Hospital Units"[mesh] OR "Hospitals"[mesh]))**)**

EMBASE search

(((exp *"Metabolomics"/ OR "Metabolomics".ti OR "metabolites".ti OR "metabolite".ti OR "Metabolomic".ti OR exp *"Metabolome"/ OR "Metabolome".ti OR "Metabolom*".ti OR "Metabolic Profile".ti OR "Metabolic Profiles".ti) AND (exp *"Nutritional status"/ OR "Nutritional status".ti OR "Nutrition status".ti OR exp *"Malnutrition"/ OR "Malnutrition".ti OR "Nutritional Deficiency".ti OR "Nutritional Deficiencies".ti OR "Undernutrition".ti OR "Malnourishment".ti OR "Malnourish*".ti OR "Ascorbic Acid Deficiency".ti OR "Ascorbic Acid Deficient".ti OR "Avitaminosis".ti OR "Beri beri".ti OR "Beriberi".ti OR "Choline Deficiency".ti OR "Choline Deficient".ti OR "Chronic Kidney Disease-Mineral and Bone Disorder".ti OR "Deficiency Disease".ti OR "Deficiency Diseases".ti OR "Folic Acid Deficiency".ti OR "Folic Acid Deficient".ti OR "Hyperhomocysteinaemia".ti OR "Hyperhomocysteinemia".ti OR "Hyperhomocysteinemia".ti OR "Kwashiorkor".ti OR "Magnesium Deficiency".ti OR "Magnesium Deficient".ti OR "Osteomalacia".ti OR "Pellagra".ti OR "Pernicious Anaemia ".ti OR "Pernicious Anemia ".ti OR "Potassium Deficiency".ti OR "Potassium Deficient".ti OR "Protein Deficiency".ti OR "Protein Deficient".ti OR "Refeeding Syndrome".ti OR "Riboflavin Deficiency".ti OR "Riboflavin Deficient".ti OR "Rickets".ti OR "Scurvy".ti OR "Severe Acute Malnutrition".ti OR "Starvation".ti OR "Steatitis".ti OR "Subacute Combined Degeneration".ti OR "Swayback".ti OR "Thiamine Deficiency".ti OR "Thiamine Deficient".ti OR "Vitamin A Deficiency".ti OR "Vitamin A Deficient".ti OR "Vitamin B 12 Deficiency".ti OR "Vitamin B 12 Deficient".ti OR "Vitamin B 6 Deficiency".ti OR "Vitamin B 6 Deficient".ti OR "Vitamin B Deficiency".ti OR "Vitamin B Deficient".ti OR "Vitamin D Deficiency".ti OR "Vitamin D Deficient".ti OR "Vitamin E Deficiency".ti OR "Vitamin E Deficient".ti OR "Vitamin K Deficiency".ti OR "Vitamin K Deficiency Bleeding".ti OR "Vitamin K Deficient".ti OR "Wernicke Encephalopathy".ti) NOT ((exp "Animals"/ OR "veterinary".ti OR "rabbit".ti OR "rabbits".ti OR "animal".ti OR "animals".ti OR "mouse".ti OR "mice".ti OR "rodent".ti OR "rodents".ti OR "rat".ti OR "rats".ti OR "pig".ti OR "pigs".ti OR "porcine".ti OR "horse".ti OR "horses".ti OR "equine".ti OR "cow".ti OR "cows".ti OR "bovine".ti OR "goat".ti OR "goats".ti OR "sheep".ti OR "ovine".ti OR "canine".ti OR "dog".ti OR "dogs".ti OR "feline".ti OR "cat".ti OR "cats".ti) NOT exp "Humans"/) AND (exp *"Patient"/ OR "hospitalized".ti,ab OR "hospitalised".ti,ab OR "patients".ti,ab OR "patient".ti,ab OR exp *"Patient Care"/ OR exp *"Hospital"/)) **OR** ((exp *"Malnutrition"/ OR "Malnutrition".ti OR "Nutritional Deficiency".ti OR "Nutritional Deficiencies".ti OR "Undernutrition".ti OR "Malnourishment".ti OR "Malnourish*".ti OR "Ascorbic Acid Deficiency".ti OR "Ascorbic Acid Deficient".ti OR "Avitaminosis".ti OR "Beri beri".ti

OR "Beriberi".ti OR "Choline Deficiency".ti OR "Choline Deficient".ti OR "Chronic Kidney Disease-Mineral and Bone Disorder".ti OR "Deficiency Disease".ti OR "Deficiency Diseases".ti OR "Fetal Nutrition Disorders".ti OR "Folic Acid Deficiency".ti OR "Folic Acid Deficient".ti OR "Hyperhomocysteinaemia".ti OR "Hyperhomocysteinemia".ti OR "Hyperhomocysteinemia".ti OR "Kwashiorkor".ti OR "Magnesium Deficiency".ti OR "Magnesium Deficient".ti OR "Osteomalacia".ti OR "Pellagra".ti OR "Pernicious Anaemia ".ti OR "Pernicious Anemia ".ti OR "Potassium Deficiency".ti OR "Potassium Deficient".ti OR "Protein Deficiency".ti OR "Protein Deficient".ti OR "Refeeding Syndrome".ti OR "Riboflavin Deficiency".ti OR "Riboflavin Deficient".ti OR "Rickets".ti OR "Scurvy".ti OR "Severe Acute Malnutrition".ti OR "Starvation".ti OR "Steatitis".ti OR "Subacute Combined Degeneration".ti OR "Swayback".ti OR "Thiamine Deficiency".ti OR "Thiamine Deficient".ti OR "Vitamin A Deficiency".ti OR "Vitamin A Deficient".ti OR "Vitamin B 12 Deficiency".ti OR "Vitamin B 12 Deficient".ti OR "Vitamin B 6 Deficiency".ti OR "Vitamin B 6 Deficient".ti OR "Vitamin B Deficiency".ti OR "Vitamin B Deficient".ti OR "Vitamin D Deficiency".ti OR "Vitamin D Deficient".ti OR "Vitamin E Deficiency".ti OR "Vitamin E Deficient".ti OR "Vitamin K Deficiency".ti OR "Vitamin K Deficiency Bleeding".ti OR "Vitamin K Deficient".ti OR "Wernicke Encephalopathy".ti) AND (exp *"Nutritional status"/ OR "Nutritional status".ti OR "Nutrition status".ti OR exp *"Nutritional Assessment"/ OR "Nutrition Assessment".ti OR "Nutritional Assessment".ti) AND (exp *"Vitamin"/ OR "Vitamins".ti OR "Vitamin".ti OR "Vitamin A".ti OR "Vitamin B 12".ti OR "Vitamin B 6".ti OR "Vitamin D".ti OR "Vitamin E".ti OR "Vitamin K".ti OR "Vitamin K 1".ti OR "Vitamin K 2".ti OR "Vitamin K 3".ti OR "Vitamin U".ti OR *"1 alpha-hydroxyergocalciferol"/ OR *"24,25-Dihydroxyvitamin D 3"/ OR *"25-Hydroxyvitamin D 2"/ OR *"7-dehydrocholesterol"/ OR *"Acetylcarnitine"/ OR *"alpha-cryptoxanthin"/ OR *"alpha-Tocopherol"/ OR *"aminopyrine, dexamethasone, phenylbutazone, thiamine, vitamin B12 drug combination"/ OR *"Ascorbic Acid"/ OR *"beta Carotene"/ OR *"Beta-Cryptoxanthin"/ OR *"beta-Tocopherol"/ OR *"Biotin"/ OR *"Calcifediol"/ OR *"Calcitriol"/ OR *"calcium ascorbate"/ OR *"Cholecalciferol"/ OR *"choline, dehydrocholic acid, magnesium orotate, orotic acid, Vitamin B12 drug combination"/ OR *"Cobamides"/ OR *"Cod Liver Oil"/ OR *"coenzyme Q10"/ OR *"Dehydroascorbic Acid"/ OR *"Dehydrocholesterols"/ OR *"Dihydrotachysterol"/ OR *"Dihydroxycholecalciferols"/ OR *"Ergocalciferols"/ OR *"Ergosterol"/ OR *"Flavin Mononucleotide"/ OR *"Folic Acid"/ OR *"Formyltetrahydrofolates"/ OR *"Fursultiamin"/ OR *"gamma-Tocopherol"/ OR *"Hydroxocobalamin"/ OR *"Hydroxycholecalciferols"/ OR *"Inositol"/ OR *"Leucovorin"/ OR *"Niacin"/ OR *"Niacinamide"/ OR

*"Nicorandil"/ OR *"Nicotinic Acids"/ OR *"Palmitoylcarnitine"/ OR *"Pantothenic Acid"/ OR *"provitamin C"/ OR *"Pteroylpolyglutamic Acids"/ OR *"Pyridoxal"/ OR *"Pyridoxal Phosphate"/ OR *"Pyridoxamine"/ OR *"Pyridoxine"/ OR *"Riboflavin"/ OR *"sapotexanthin"/ OR *"Tetrahydrofolates"/ OR *"Thiamine"/ OR *"Thiamine Monophosphate"/ OR *"Thiamine Pyrophosphate"/ OR *"Thiamine Triphosphate"/ OR *"Thioctic Acid"/ OR *"Tocopherols"/ OR *"Tocotrienols"/ OR *"Tocovid"/ OR *"Vitamin A"/ OR *"vitamin A, pentifyllin, nicotinic acid, and vitamin E combination"/ OR *"Vitamin B 12"/ OR *"Vitamin B 6"/ OR *"Vitamin D"/ OR *"Vitamin E"/ OR *"Vitamin K"/ OR *"Vitamin K 1"/ OR *"Vitamin K 2"/ OR *"Vitamin K 3"/ OR *"Vitamin U"/ OR exp *"Antioxidant"/ OR "Antioxidant".ti OR "Antioxidants".ti) NOT ((exp "Animals"/ OR "veterinary".ti OR "rabbit".ti OR "rabbits".ti OR "animal".ti OR "animals".ti OR "mouse".ti OR "mice".ti OR "rodent".ti OR "rodents".ti OR "rat".ti OR "rats".ti OR "pig".ti OR "pigs".ti OR "porcine".ti OR "horse".ti OR "horses".ti OR "equine".ti OR "cow".ti OR "cows".ti OR "bovine".ti OR "goat".ti OR "goats".ti OR "sheep".ti OR "ovine".ti OR "canine".ti OR "dog".ti OR "dogs".ti OR "feline".ti OR "cat".ti OR "cats".ti) NOT exp "Humans"/) AND (exp *"Patient"/ OR "hospitalized".ti,ab OR "hospitalised".ti,ab OR "patients".ti,ab OR "patient".ti,ab OR "Patient Care"/ OR exp *"Hospital"/))) NOT (conference review or conference abstract).pt