Cytokines and Biomarkers of Cancer Cachexia and their Relationship to Markers of Nutritional Status, Inflammation and Quality of life

Lipshitz M,[1,2] Visser J,[1] Anderson R,[3] Nel DG,[4] Smit T,[5] Steel H,[3] Rapoport B,[3,5]

[1]Division of Human Nutrition, Stellenbosch University, South Africa [2]Melanie Levy Dietician, Johannesburg, South Africa [3]Department of Immunology, University of Pretoria, South Africa [4]Centre for Statistical Consultation, Stellenbosch University, South Africa [5]The Medical Oncology Centre of Rosebank, Johannesburg, South Africa,

Introduction and Aim

- Cancer cachexia can cause more than 20% of deaths in cancer with **sarcopenia and Quality of Life (QoL)**, independently predicting survival.
- Cachexia research suggests that biomarkers of cachexia are related to QoL and nutritional status however, the **ideal biomarker** for cachexia assessment, prognosis and blockade remains to be identified.
- **Emerging biomarkers** require baseline research of their relationships to cachexia and sarcopenia.
- The aim of the study was: i) to **establish differences** in biomarkers of cachexia, nutritional status and QoL between patients with cancer cachexia and healthy matched controls, ii) to explore the **relationships and correlations** of these markers to nutritional status and QoL.

***Long-term aim:* to improve knowledge of the relationships between emerging biomarkers of cancer cachexia, nutritional status and QoL so that future treatments may target cachexia and ultimately prognosis.**

Methods

- Prospective case-control study: including 40 patients with advanced cancer, mixed diagnoses and 40 gender, age-matched controls.
- Nutritional status was assessed using sarcopenia [skeletal muscle index (SMI) from bioelectrical impedance] and QoL was measured using the European Organization for the Research and Treatment of Cancer Quality of Life-C30 assessment (EORTC-QLQ-C30).
- Biomarkers assessed: albumin, haemoglobin (Hb), neutrophils, lymphocytes, platelets, C-reactive protein (CRP), tumor necrosis factor alpha (TNFα), Interleukin-6 (IL-6), Interleukin-8 (IL-8), C-X-C motif chemokine ligand 5 (CXCL5) and citrullinated histone H3 (H3Cit).
- Descriptive statistics & regression analyses for correlations were undertaken, using Receiver Operator Characteristic (ROC) curve analysis to determine reference values for the group.

Results

- 43% of percent of cases were **sarcopenic** with a significantly lower SMI [6.67kg/m^2 (±1.34) vs. 7.67kg/m^2 (±1.08), p=<0.01] compared to controls **(Figure 1).**
- For all sectors of **QoL assessment**: QoL [Global Status (QL-G), Functional Scales (QL-FS) and Symptom Scales (QL-SS)] cases scored significantly different (p<0.01) compared to reference values.
- Significant differences were found for albumin, lymphocytes, platelets, haemoglobin, platelet to lymphocyte ratio (PLR), systemic immune-inflammation index (SII), CRP, TNFα, all at p<0.01, neutrophil to lymphocyte ratio (NLR) (p=0.02), IL-6 (p<0.04) and IL-8 (p=0.02) between cases and controls **(Table 1).**
- No difference was found for **CXCL5** (p=0.22) or **H3Cit** (p=0.99) between the groups.
- **ROC curve analysis** indicated that CXCL5 (0.59) and H3Cit (0.56) ranked the lowest of all markers **(Figure 2)** while PLR, CRP and TNFα were the top ranking biomarkers with areas under the curve (AUC) of 0.84, 0.80 and 0.79 respectively.

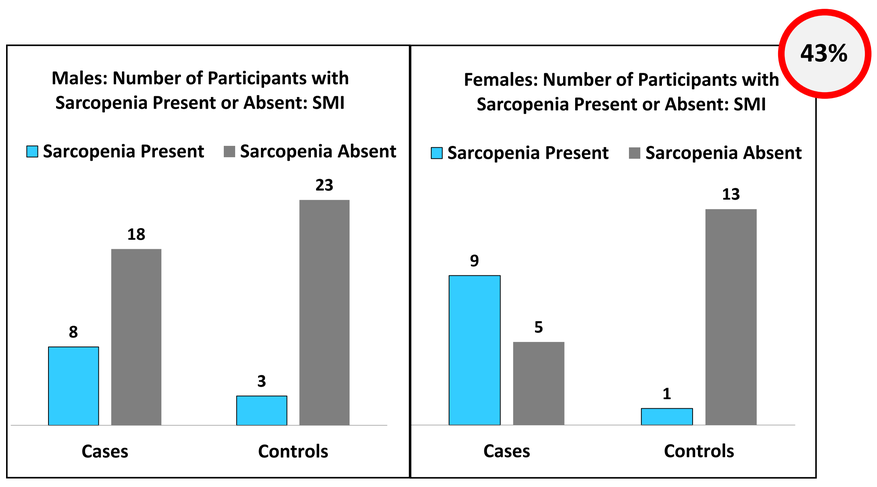

Figure 1: Presence of sarcopenia according to Skeletal Muscle Index (SMI)

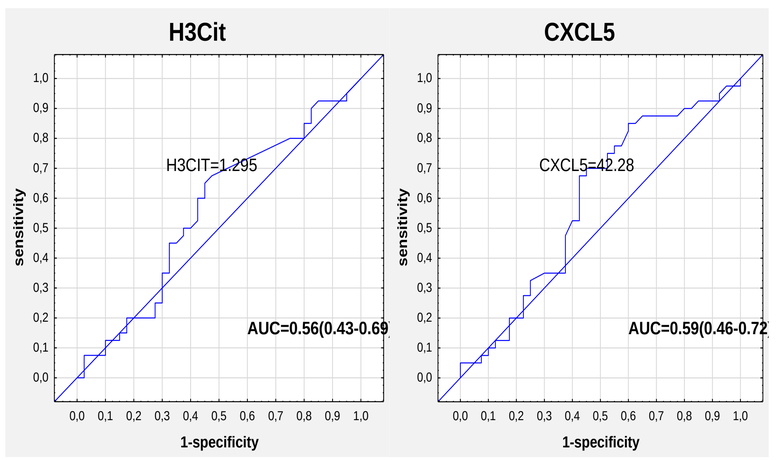

Figure 2: Receiver Operating Characteristic (ROC) curves for cut-offs: H3Cit and CXCL5

- For SMI, biomarkers that showed significance to the presence or absence of sarcopenia were albumin (p=0.03), Hb (p=0.008) and TNFα (p=0.036) **(Figure 3).**
- Only albumin, NLR, Hb, PLR, SII, TNFα, IL-8 and CRP showed significant correlations to all three QoL sectors **(Table 2).**
- Using cut-offs for biomarkers and categories for sarcopenia CRP was significantly related to the presence and absence of sarcopenia (p=0.007) **(Figure 4).**
- Using cut-offs for biomarkers and QL-FS, CXCL5 significantly correlated to QL-FS (p=0.04) **(Figure 6).**

Table 1: Summary of biomarker analysis results

Marker	Reference Ranges	Cases	Controls	P-value (Cases vs. Controls)	P-value (Cases vs. Reference Constant)
Albumin (g/L)	35-50	39.66 (±6.41)	46.99 (±2.21)	P < 0.01	
Hb (g/dL)	13.8-18.8	12.38 (±2.04)	15.13 (±0.92)	P < 0.01	
NLR	2.73	4.85 (±6.59)	2.31 (±1.10)	P = 0.02	P = 0.008
PLR	148.82	232.90 (±119.70)	119.18 (±34.63)	P < 0.01	P < 0.001
SII	791.96	1387.35 (±1866.47)	543.54 (±301.74)	P < 0.01	P = 0.051
CRP (mg/L)	2.775	31.65 (±56.54)	2.78 (±6.72)	P < 0.01	P = 0.002
TNFα (pg/mL)	20.745	43.52 (±52.77)	15.69 (±13.51)	P < 0.01	P = 0.009
IL-6 (pg/mL)	4.39	41.13 (±6.87)	35.64 (±69.07)	P = 0.04	P < 0.001
IL-8 (pg/mL)	9.175	33.08 (±59.90)	29.85 (±81.53)	P = 0.02	P = 0.023
CXCL5 (pg/mL)	42.28	91.37(±140.30)	61.74 (±59.01)	P = 0.22	P = 0.033
H3Cit (ng/mL)	1.295	2.38(±2.88)	2.38 (±6.72)	P = 0.99	P = 0.023

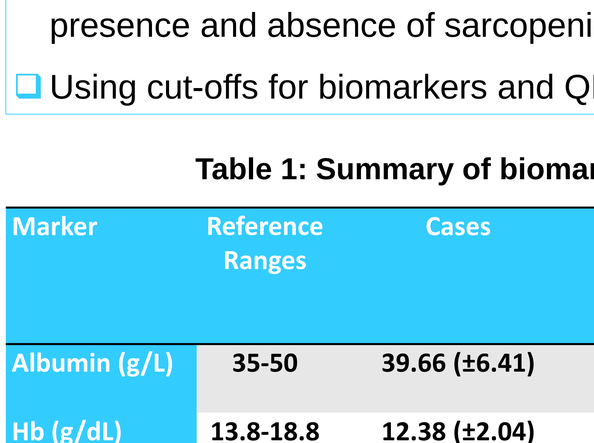

Figure 4: CXCL5 correlations to QL-FS

Table 2 : Biomarkers with significant correlations to QoL sectors

Biomarker	QoL-G	QoL-FS	QoL-SS
Albumin	+	+	-
Hb	+	+	-
NLR	-	NO SIG	+
PLR	-	-	+
SII	-	-	+
TNFα	-	-	+
IL-8	-	-	+
CRP	-	-	+

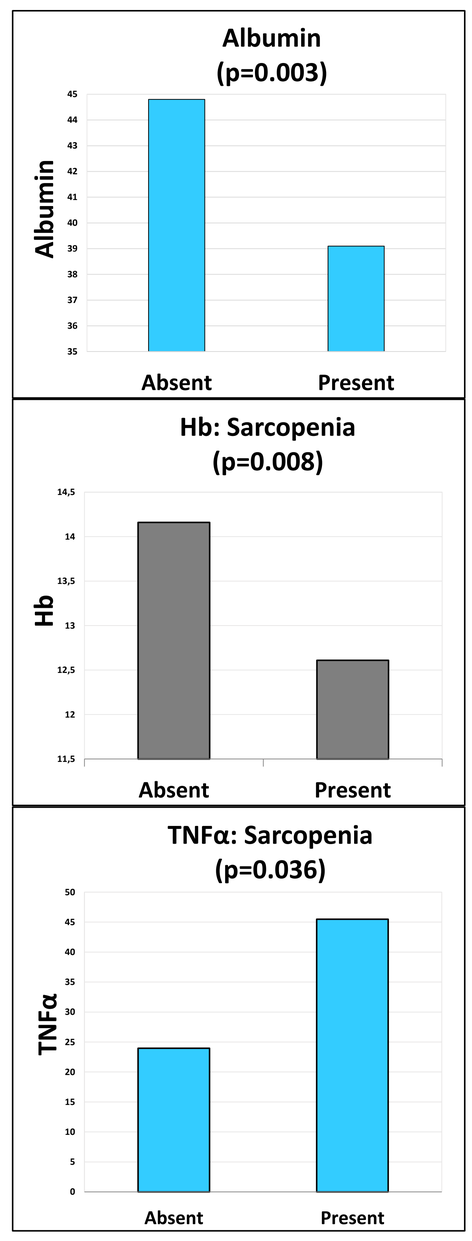

Figure 3: Biomarkers showing significance to the presence of sarcopenia

Conclusions

- CRP, albumin and haemoglobin consistently showed baseline differences between cases and controls and in further correlations to nutritional status and QoL.
- NLR, PLR, SII, TNFα, IL-6 and IL-8 showed inconsistent correlations of significance to baseline assessments.
- **Emerging biomarkers CXCL5 and H3Cit were not found to be reliable biomarkers for cancer cachexia in defining correlations to nutritional status and QoL.**