
2018
VIENNA, AUSTRIA
SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE
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Faculty Disclosure

X	No, nothing to disclose
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Leptin as a predictive biomarker for the onset of cancer-related fatigue (CRF): A prospective cohort study

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Background

- Cancer-related fatigue (CRF) is defined as distressing, persistent exhaustion that is not proportionate to recent activity and interferes with usual functioning[1].

- While commonly proposed to be mediated by pro-inflammatory cytokines, the underlying pathophysiology behind CRF remains poorly understood [2].

1. NCCN Guidelines. Cancer-related fatigue. Version 2.2017
2. Cruz et al. Clinical and Translational Medicine

Leptin

Brain

Decrease food intake

Leptin

Cancer-related Fatigue

Higher leptin concentration correlated with **greater fatigue levels** in cohort of patients with:

cardiovascular risk factors [4]
chronic hepatitis C infection [5,6]
irritable bowl syndrome [7]

Study Objective: To correlate **plasma leptin levels** with **fatigue levels** in early-stage breast cancer patients

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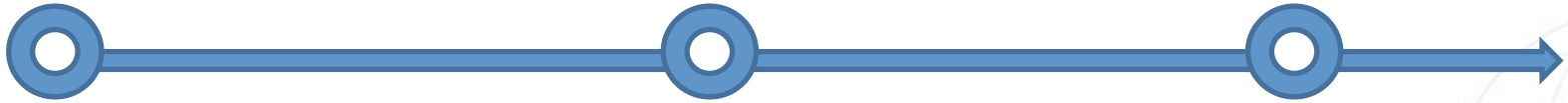
Study Design

- Prospective cohort of early-stage breast cancer patients
- Conducted from 2014-2017
- Inclusion and Exclusion Criteria
- Approved by Singhealth Institutional Review Board (CIRB 2014/754/B)
- Written Informed Consent was obtained prior to patient's participation

T1: baseline and prior to chemotherapy

T2: during chemotherapy

T3: 12 weeks after baseline



Study Design

Questionnaire

Not at all	A little	Moderately	Quite a bit	Extremely
0	1	2	3	4

Blood draw

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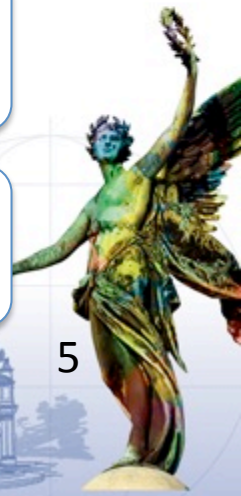
Multi-Dimensional Fatigue Symptom Inventory-Short Form (MFSI-SF)

EORTC-QLQ C-30

- Locally validated questionnaire for its psychometric properties, measurement equivalence[8]
- Multi-dimensional, consisting of **5 sub-domains**: general, physical, mental, emotional and vigor
- CRF status defined as an increase of **10.8 points** based on pre-determined minimal clinically important difference (MCID) range[9]

Luminex bead-immunoassay

Panel of cytokines (TNF-α, IL-6 and IL-8) and leptin levels



8. Chan A et al, Health Qual Life Outcomes 2018;16:20
9. Chan A et al, J Pain Symptom Manage 2018;55:992-997

Cohort Characteristics

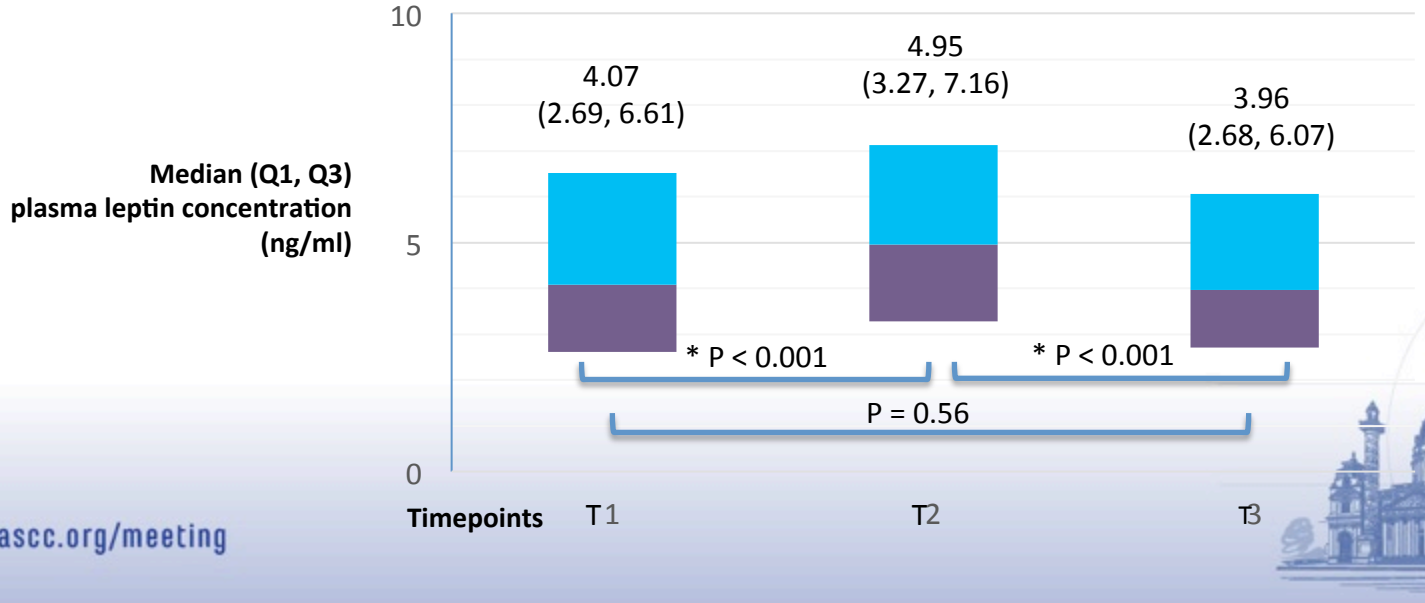
Characteristics (n=136)		Mean ± SD / Frequency (%)
Age (years)		51.5 ± 8.8
BMI (kg/m^2)		23.9 ± 4.1
Ethnicity	Chinese	112 (82.4)
	Malay	12 (8.8)
	Indian	7 (5.15)
	Others	5 (3.7)
Breast Cancer Stage	I	15 (11.0)
	II	92 (67.6)
	III	29 (21.3)

ECOG Performance Status	0	132 (97.1)
	1	4 (2.9)
Baseline Haemoglobin Level	< 12 g/dL	35 (25.7)
	> 12 g/dL	101 (74.3)
Menopausal Status	Pre	69 (50.7)
	Post	67 (49.3)
Chemotherapy Regimen	Anthracycline-based	94 (69.1)
	Non anthracycline-based	42 (30.9)

Biomarkers

Timepoints	T1	T2	T3
Proportion of patients with CRF (%)	**N/A**	**13.2%**	**22.1%**

Figure 1: Graph of plasma leptin concentration against time points (T1-T3)



Univariate analysis with other adipokines

	Sub-Domains of MFSI-SF					MFSI-SF Total Score β (SE)
Biomarker	General	Physical	Emotional	Mental	Vigor	
Leptin (ng/mL)	-0.16 (0.017)	-0.022 (0.045)	-0.11 (0.012)	-0.06 (0.025)	0.16 (0.091)	-0.56 (0.13)
IL-6	0.26 (0.152)	0.211 (0.128)	0.041 (0.102)	0.209 (0.125)	0.065 (0.134)	0.226 (0.375)
IL-8	0.121 (0.105)	0.11 (0.091)	0.003 (0.089)	0.041 (0.071)	0.076 (0.139)	0.079 (0.079)
TNF-α	0.0035 (0.0045)	-0.0027 (0.0012)	-0.0042 (1.14e-8)	-0.0035 (0.0004)	0.0075 (0.005)	-0.012 (0.011)

- There could be possibility of leptin-cytokine crosstalk[10] .

Adjusted models

	Covariates adjusted for	MFSI-SF Total Score β (SE)	P-value
Leptin (ng/mL)		-0.564 (0.132)	<0.01
Adjusted Model 1	anxiety, depression and insomnia	-0.211 (0.042)	<0.01
Adjusted Model 2	anxiety, depression, insomnia **and** TNF-α	-0.225 (0.040)	<0.01

- Models were fitted to control for known confounders and TNF-α
- Leptin retained statistically significant correlation **(β)** with fatigue levels, albeit to a smaller extent.

Conclusion

- Plasma leptin levels showed a statistically significant **inverse correlation** with CRF over time.
- This suggests that the underlying mechanism linking leptin to fatigue may be preceded by **other non-inflammatory factors**.
- Future studies may evaluate sensitivity and specificity of plasma leptin level as a fatigue biomarker to confer its clinical utility.

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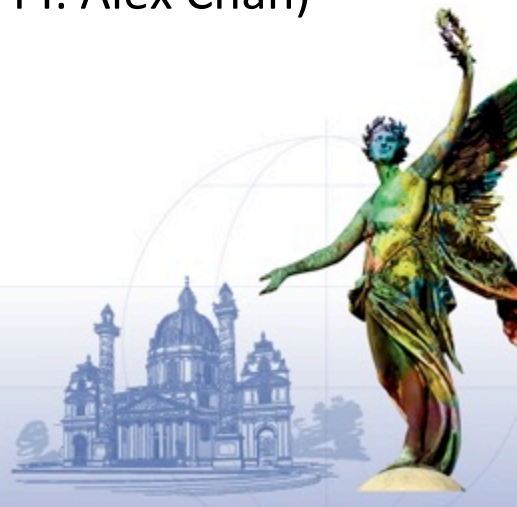


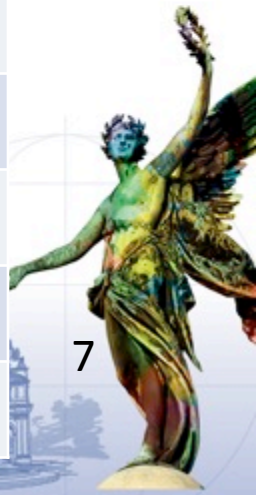
Biomarkers

	Median (Q1, Q3)			P-values for Wilcoxon Sign Rank Test		
Biomarker (ng/mL)	**T1**	**T2**	**T3**	**T1-T2**	**T1-T3**	**T2-T3**
Leptin	4.07 (2.69, 6.61)	4.95 (3.27,7.16)	3.96 (2.68, 6.07)	**P < 0.001**	0.56	**P < 0.001**
IL-1b	0.27 (0.13, 0.44)	0.20 (0.11, 0.43)	0.30 (0.14, 0.52)	0.37	0.06	**P < 0.001**
IL-4	0.31 (0.19, 0.68)	0.36 (0.21, 0.73)	0.46 (0.28, 0.73)	**P < 0.05**	**P < 0.001**	0.068
IL-6	0.80 (0.36, 1.72)	1.12 (0.56, 2.46)	1.27 (0.52, 2.60)	**P < 0.001**	**P < 0.001**	0.06
IL-8	3.70 (2.29. 4.95)	3.34 (2.25, 5.06)	3.69 (2.48, 5.28)	0.42	**P < 0.05**	**P < 0.001**
IFN	7.98 (0.88, 19.85)	6.78 (1.20, 18.09)	8.86 (1.65, 27.50)	0.89	**P < 0.001**	**P < 0.05**
TNF-α	6.41 (2.76, 15.15)	6.95 (3.22, 18.61)	8.27 (2.71, 19.71)	0.78	**P < 0.001**	**P < 0.001**

Univariate analysis

	Sub-Domains					MFSI-SF Total Score β (SE)
Biomarker (ng/mL)	General	Physical	Emotional	Mental	Vigor	
Leptin	**-0.16 (0.017)**	-0.022 (0.045)	**-0.11 (0.012)**	-0.06 (0.025)	0.16 (0.091)	**-0.56 (0.13)**
IL-1b	**2.66 (1.01)**	1.45 (0.76)	**2.59 (0.95)**	0.77 (0.65)	-0.81 (0.89)	**13.43 (5.14)**
IL-4	**-1.02 (0.21)**	-0.049 (0.378)	-0.49 (0.32)	-0.13 (0.304)	**1.66 (0.69)**	-49.4 (133.7)
IL-6	**0.47 (0.18)**	**0.52 (0.16)**	**0.37 (0.18)**	0.19 (0.12)	0.095 (0.145)	21.97 (28.39)
IL-8	**0.203 (0.101)**	0.106 (0.081)	0.13 (0.092)	-0.013 (0.067)	0.120 (0.134)	**-18.53 (4.65)**
IFN	**0.048 (0.021)**	**0.049 (0.018)**	0.037 (0.021)	0.028 (0.016)	-0.015 (0.023)	-0.121 (0.30)
TNF-α	-0.029 (0.002)	0.002 (0.0018)	0.031 (0.016)	**-0.003 (0.0002)**	0.0073 (0.007)	-0.280 (1.00)

*** Bolded are those with p-value < 0.05**



Univariate analysis of a list of individual, possible explanatory variables that were clerked: BMI ($p = 0.128$), Hb ($p = 0.593$), stage of disease ($p = 0.099$), age_range ($p < 0.01$) menopausal status ($p = 0.035$), ECOG ($p = 0.65$) chemoregime ($p < 0.01$) etc

while some of these may happen to be known cofounders, may have too many, so significant p-value is used as selection criteria*

But only those which showed p-value < 0.05 were added into the final model to adjust for effects of leptin in relation to MFSI, and leptin showed attenuated coefficients in the face of the other covariates but still hold out and retained its statistical significance

Univariate analysis with other adipokines

	Sub-Domains					MFSI-SF Total Score β (SE)
Biomarker (ng/mL)	General	Physical	Emotional	Mental	Vigor	
Leptin	**-0.16 (0.017)**	-0.022 (0.045)	**-0.11 (0.012)**	**-0.06 (0.025)**	0.16 (0.091)	**-0.56 (0.13)**

- Correlated across time points using generalised estimating equation (GEE) model
- There could be possibility of leptin-cytokine crosstalk[7]

*** B**

7. Newman G et al. Mol Cell Endocrinol 2014; 25:570-582

Univariate analysis with confounders

	Sub-Domains					MFSI-SF Total Score β (SE)
	General	Physical	Emotional	Mental	Vigor	
Leptin	**-0.16 (0.017)**	-0.022 (0.045)	**-0.11 (0.012)**	-0.06 (0.025)	0.16 (0.091)	**-0.56 (0.132)**
Anxiety	**0.29 (0.035)**	**0.24 (0.031)**	**0.265 (0.033)**	**0.17 (0.027)**	**-0.23 (0.018)**	**1.38 (0.126)**
Depression	**0.44 (0.046)**	**0.28 (0.039)**	**0.31 (0.400)**	**0.16 (0.031)**	**-0.505 (0.038)**	**1.85 (0.141)**
Insomnia	**0.014 (0.006)**	**0.023 (0.006)**	0.0075 (0.006)	0.011 (0.0046)	**-0.026 (0.008)**	**0.076 (0.025)**

*** Bolded are those with p-value < 0.05**

Adjusted models

	Covariates adjusted for	MFSI-SF Total Score β (SE)	P-value
Leptin (ng/mL)		**-0.564 (0.132)**	**<0.01**
Adjusted Model 1	anxiety, depression and insomnia	**-0.211 (0.042)**	**<0.01**
Adjusted Model 2	anxiety, depression, insomnia **and** TNF-α	**-0.225 (0.040)**	**<0.01**
Adjusted model 3	anxiety, depression, insomnia **and** age range ≥ 65, menopausal status and chemotherapy type	**-0.222 (0.041)**	**<0.01**

Leptin retained statistically significant correlation **(β)** with fatigue levels, albeit to a smaller extent when adjustments have been made