

HUBUNGAN SINDROMA METABOLIK, OBESITAS, DAN KESINTASAN PASIEN KANKER PAYUDARA SUB-TIPE MOLEKULER HR+/HER2- NON-METASTATIK
Kajian pada Biomarka Metabolik, Mitogenik, dan Epigenetik: Leptin, miR-222-3p, dan miR-143-3p
KARTIKA WIDAYATI, Prof.Dr.dr. Teguh Aryandono, SpB.(K).Onk; dr. Mardiah S. Hardianti, PhD., SpPD-KHOM
HUBUNGAN SINDROMA METABOLIK, OBESITAS, DAN KESINTASAN PASIEN KANKER PAYUDARA SUB-TIPE MOLEKULER HR+/HER2- NON-METASTATIK

Kajian terhadap Biomarka Metabolik, Mitogenik, dan Epigenetik:
Leptin, miR-222-3p, dan miR-143-3p

Kartika W. Taroeno-Hariadi^{1,2}, Mardiah S. Hardianti², Teguh Aryandono³

¹ Program Doktor Ilmu Kedokteran dan Kesehatan, ² Sub Bagian Hematologi dan Onkologi Medik, Bagian Ilmu Penyakit Dalam, ³ Sub Bagian Bedah Onkologi, Bagian Ilmu Bedah
Fakultas Kedokteran, Kesehatan Masyarakat, dan Keperawatan, Universitas Gadjah Mada, Yogyakarta;
RSUP dr Sardjito, Yogyakarta.

ABSTRAK

Latar Belakang Sindroma metabolik (MetS) dan obesitas sering dikaitkan dengan munculnya berbagai penyakit termasuk kanker payudara. Kanker payudara dengan ekspresi reseptor hormon positif tanpa ekspresi *human epidermal growth factor receptor-2* (HR+/HER2-) diketahui memiliki prognosis paling baik. Pengaruh metabolik terhadap kesintasan pasien kanker payudara HR+/HER2- belum diketahui.

Tujuan Penelitian ini bertujuan menguji hubungan MetS dan obesitas dengan kesintasan kanker payudara HR+/HER2- serta menguji apakah leptin, miR-222-3p, dan miR-143-3p yang berperan pada proses metabolik dan mitogenik berhubungan dengan kesintasan kanker sub-tipe tersebut.

Metode Penelitian dilakukan secara kohort retrospektif dengan mengambil data rekam medis pasien mulai tahun 2010-2020. Kriteria inklusi adalah tipe karsinoma invasif, stadium non-metastatik, IHC HR+/HER2-, sudah mendapat terapi hormon minimal 6 bulan sebelum dilakukan inklusi, menyelesaikan siklus terapi ajuvan lengkap, memiliki data *surveillance* evaluasi tumor setiap 6 bulan, dan memiliki data profil lemak, dan antropometrik pasca diagnosis. Data klinis semua ditarik dari rekam medis.

MetS ditentukan berdasar kriteria NCEP-ATP III dengan modifikasi Asia. Obesitas ditentukan dengan kriteria Asia Pasifik. Leptin diperiksa dengan metode imunohistokimia. Kuantifikasi miR-222-3p dan miR-143-3p dilakukan secara RT-qPCR.

MetS, obesitas, leptin, miR-222-3p, miR-143-3p bersama-sama parameter klinikopatologis dianalisis hubungannya terhadap *Disease-Free Survival* (DFS), dan *Overall Survival* (OS).

Data dianalisis dengan Chi-square, Fisher exact test, Cox-proportional hazard model, dan Kaplan-Meier dengan signifikansi $p < 0,05$.

Hasil Terdapat 223 kasus kanker payudara HR+/HER2-. MetS dijumpai pada 56,1% kasus. MetS tidak mempengaruhi kesintasan. Obesitas berdasarkan BMI ≥ 25 juga tidak mempengaruhi kesintasan. Obesitas visceral (WHR $\geq 0,85$) berkaitan dengan DFS singkat (HR 1,563; $p = 0,073$) dan OS singkat (HR 4,281; $p = 0,028$).

Seratus tiga puluh enam blok parafin dari 223 kasus diperiksa marka molekuler. *Over-ekspresi* leptin tidak berhubungan dengan DFS (HR 0,592, $p = 0,099$). *Over-ekspresi* miR-222-3p berkaitan dengan DFS (HR 0,350; $p = 0,018$) dan OS (HR 0,028; $p = 0,309$) yang lebih baik. *Over-ekspresi* miR-143-3p tidak berhubungan dengan DFS (HR 0,588; $p = 0,089$). Triple *over-*



UNIVERSITAS
GADJAH MADA

HUBUNGAN SINDROMA METABOLIK, OBESITAS, DAN KESINTASAN PASIEN KANKER PAYUDARA SUB-TIPE MOLEKULER

HR+/HER2- NON-METASTATIK

Kajian pada Biomarka Metabolik, Mitogenik, dan Epigenetik: Leptin, miR-222-3p, dan miR-143-3p
KARTIKA WIDAYATI, Prof.Dr.dr. Teguh Aryandono, SpB.(K).Onk; dr. Mardiah S. Hardianti, PhD., SpPD-KHOM
Universitas Gadjah Mada, 2021 | Diunduh dari <http://etd.repository.ugm.ac.id/>
ekspresi-(leptin/miR-222-3p/miR-143-3p) merupakan penanda DFS lebih panjang (HR 0,086; $p = 0,018$).

Kesimpulan MetS tidak berhubungan dengan kesintasan kanker payudara HR+/HER2-
Obesitas visceral berhubungan dengan kesintasan lebih singkat. Over-ekspresi leptin tidak berhubungan dengan DFS. Over-ekspresi miR-222-3p berhubungan dengan kesintasan yang lebih panjang,. Over-ekspresi miR-143-3p tidak berhubungan DFS. Triple *over-ekspresi* leptin/miR-222-3p/miR-143-3p memiliki DFS yang paling panjang.

Kata kunci: *breast cancer, luminal, metabolic syndrome, microRNA, obesity, prognosis*

THE ASSOCIATION OF METABOLIC SYNDROME, OBESITY, AND SURVIVAL OF PATIENTS WITH HR+/HER2- NON-METASTATIC BREAST CANCER

The role of metabolic, mitogenic, and epigenetic markers of Leptin, miR-222-3p, and miR-143-3p

Kartika W. Taroeno-Hariadi^{1,2}, Mardiah S. Hardianti², Teguh Aryandono³

¹ Doctorate Program, ² Div. Hematology and Medical Oncology, Department of Internal Medicine, ³ Div. of Surgical Oncology, Department of Surgery, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada – Dr Sardjito Hospital, Yogyakarta

ABSTRACT

Background Metabolic syndrome (MetS) and obesity are often associated with a risk of developing various diseases including breast cancer. Breast cancer with positive hormone receptor, negative human epidermal growth factor-2 (HR+/HER2-) sub-type has an excellent prognosis. The role of MetS and obesity on survival of breast cancer with less-aggressive sub-type has not been established yet, as well as the role of metabolic, mitogenic, and epigenetic markers such as leptin, miR-222-3p, and miR-143-3p. The aim of the study was to investigate the association of MetS, obesity, leptin, miR-222-3p and miR-143-3p as prognostic markers for survival of patients with HR+/HER2- breast cancer.

Method The research was conducted retrospectively by taking patient medical record data from 2010-2020. Inclusion criteria were: invasive carcinoma, non-metastatic disease, HR+/HER2- sub-type, having received hormone therapy at least 6 months before inclusion, completed adjuvant therapy, had regular tumor evaluation and surveillance every 6 months, and have lipid profile and anthropometric data before systemic treatment initiated. Clinical data were all extracted from medical records.

MetS was determined based on NCEP-ATP III criteria with Asian modifications. Obesity was determined by the Asia Pacific criteria. Leptin was examined by immunohistochemical methods. Quantification of miR-222-3p and miR-143-3p was performed by RT-qPCR.

MetS, obesity, leptin, miR-222-3p, miR-143-3p all together with clinico-pathological parameters were analyzed for their contribution on Disease-Free Survival (DFS), and Overall Survival (OS). Data were analyzed with Chi-square, Fisher's exact test, Cox regression and Kaplan-Meier for survival estimation, with $p < 0.05$ was considered as statistically significant.

Result There were 223 cases of HR+/HER2 breast cancer for analysis. MetS was found in 56,1% cases. MetS did not affect DFS nor the OS. Obesity, measured as $BMI \geq 25$, did not affect survival. Visceral obesity measured as $WHR \geq 0.85$ was associated with early recurrence (HR 1.563; $p = 0.073$) and short survival (HR 4.281; $p = 0.028$).

There were 136 paraffine embedded tissues for molecular tests. Over-expression of leptin was not associated with DFS (HR 0.592, $p = 0.099$). Over-expression miR-222-3p was related to prolonged DFS (HR 0.350; $p = 0.018$) and OS (HR 0.028; $p = 0.309$). Over-expression of miR-143-3p was not associated with DFS (HR 0.588; $p = 0.089$). Triple over-expression-(leptin/miR-222-3p/miR-143-3p) was a marker of prolonged DFS (HR 0.086; $p = 0.018$).

Conclusion MetS did not affect the survival of HR+/HER2 breast cancer. Visceral obesity was associated with poor survival. Over-expression of leptin was not significantly associated with DFS. Over-expression of miR-222-3p was a prognostic marker for good survival outcome.



UNIVERSITAS
GADJAH MADA

HUBUNGAN SINDROMA METABOLIK, OBESITAS, DAN KESINTASAN PASIEN KANKER PAYUDARA SUB-TIPE MOLEKULER

HR+/HER2- NON-METASTATIK Kajian pada Biomarka Metabolik, Mitogenik, dan Epigenetik: Leptin, miR-222-3p, dan miR-143-3p

KARTIKA WIDAYATI, Prof.Dr.dr. Teguh Aryandono, SpB.(K).Onk; dr. Mardiah S. Hardianti, PhD., SpPD-KHOM
Universitas Gadjah Mada 2021 | Diunduh dari <http://eprints.repository.ugm.ac.id/>

Over-expression of miR-143-3p was not significantly associated with DFS. Triple over-expression of leptin/miR-222-3p/miR-143-3p was associated with prolonged DFS.

Keywords: breast cancer, luminal, metabolic syndrome, microRNA, obesity, prognosis