

## ABSTRAK

**LATAR BELAKANG:** Kanker ovarium merupakan penyakit keganasan ke-3 terbanyak pada wanita Indonesia dengan prognosis yang buruk dikarenakan kesulitan dalam melakukan deteksi dini sehingga lebih banyak pasien ditemukan dalam stadium yang lebih lanjut. Beberapa penelitian terakhir telah memperkenalkan penggunaan miR-21 sebagai penanda diagnosis dan prognosis pada kanker ovarium. Hingga saat ini, belum ada penelitian yang menerangkan dinamika ekspresi miR-21 sesudah operasi dan peranannya dalam memprediksi prognosis pasien kanker ovarium epitel.

**TUJUAN:** Mengetahui perbedaan ekspresi miR-21 pada plasma darah sebelum dan sesudah operasi dan hubungannya dengan kesintasan hidup 2 tahun pasien kanker ovarium epitel di RSUP dr. Sardjito.

**MATERIAL DAN METODE:** Penelitian ini merupakan penelitian observasional dengan desain kohort retrospektif dengan menggunakan 29 sampel darah pasien kanker ovarium epitel yang diambil sebelum operasi dan 7-14 hari sesudah operasi di RSUP dr. Sardjito. Selanjutnya dilakukan isolasi RNA, sintesis cDNA, dan *Real Time qPCR* untuk mendapatkan nilai Ct miR-21 (target) dan Ct miR-16 (*reference gene*) serta perhitungan *fold change* dengan metode Livak. Analisis perbandingan miR-21 plasma sebelum dan sesudah operasi dilakukan dengan *paired t-test* SPSS, kemudian dilakukan analisis kesintasan hidup dengan kurva Kaplan Meier, Log Rank Test dan Cox Regression.

**HASIL:** Dari 29 subyek penelitian didapatkan rerata usia 48,7 tahun dimana lebih banyak pasien memiliki jenis histopatologi tipe I (66%), paritas  $\geq 1$  (52%), residu tumor  $<1\text{cm}$  (62%), terdiagnosis pada stadium I-II (55%). Ekspresi miR-21 plasma sesudah operasi ditemukan meningkat 2,1 kali dibandingkan dengan miR-21 plasma sebelum operasi namun tidak bermakna secara statistik ( $p=0,063$ ). Apabila dikategorikan menurut status klinikopatologi, tampak bahwa terdapat perbedaan signifikan miR-21 sesudah operasi dibandingkan sebelum operasi pada kategori usia  $<50$  tahun (meningkat 1,19 kali), stadium I-II (menurun 2,18 kali), residu tumor  $<1\text{cm}$  (meningkat 2,85 kali), kadar CA-125 pra operasi  $\geq 500\text{ U/ml}$  (meningkat 3,29

kali) dan paritas  $\geq 1$  (meningkat 2,99 kali). MiR-21 plasma darah pasca operasi yang meningkat (*up-regulation*) dibandingkan pra operasi berkaitan dengan prognosis yang lebih buruk, risiko kematian yang lebih tinggi dan probabilitas kesintasan hidup lebih rendah namun tidak signifikan bermakna secara statistik (HR=1,410; p=0.6254; IK=0,3510–5,667). Selain itu tipe histopatologi II dan stadium klinis yang lanjut juga memperlihatkan prognosis yang buruk terhadap kesintasan hidup. Namun setelah dilakukan analisis multivariat dengan cox regression, tampak bahwa tipe histopatologi II, stadium lanjut, residu tumor >1cm dan miR-21 sesudah operasi yang *up-regulation* bukan merupakan penanda prognosis bebas (*independent prognosis marker*) pada ketahanan hidup pasien kanker ovarium epitel.

**KESIMPULAN:** Ekspresi miR-21 sesudah operasi meningkat 2,1 kali dibandingkan sebelum operasi namun peningkatannya tidak cukup signifikan. Sementara miR-21 sesudah operasi yang meningkat (*up-regulation*) berhubungan dengan risiko kematian yang lebih besar dan prognosis yang lebih buruk sehingga miR-21 masih berpotensi untuk memprediksi prognosis pasien kanker ovarium epitel.

**KATA KUNCI:** MicroRNA-21, miR-21, MiRNA-21, sebelum operasi, sesudah operasi, klinikopatologi, prognosis, kesintasan hidup, kanker ovarium epitel.

## ABSTRACT

**BACKGROUND:** Ovarian cancer is the third most malignant disease in Indonesian women with poor prognosis due to difficulties in early detection so that more patients are found in advanced stage. Several recent studies have introduced the use of miR-21 as a diagnostic and prognostic marker of ovarian cancer. To date, there are no studies that explain the expression of miR-21 after surgery and its role in predicting the prognosis of epithelial ovarian cancer patients.

**OBJECTIVE:** To determine the differences in miR-21 expression in blood plasma before and after surgery and their relationship with 2-year survival of epithelial ovarian cancer patients at dr. Sardjito Hospital.

**MATERIALS AND METHOD:** This study is an observational study with a retrospective cohort design using 29 blood samples of epithelial ovarian cancer patients taken before surgery and 7-14 days after surgery at dr. Sardjito Hospital. Furthermore, RNA isolation, cDNA synthesis, and Real Time qPCR were carried out to obtain the Ct miR-21 (target) and Ct miR-16 (reference gene) values, then calculation of fold change using the Livak method. Comparative analysis of miR-21 plasma before and after surgery was performed with paired t-test SPSS, then performed survival analysis with Kaplan Meier curves, Log Rank Test and Cox Regression.

**RESULT:** Of the 29 study subjects, the average age was 48.7 years where more patients had type I histopathology (66%), parity  $\geq 1$  (52%), tumor residue  $< 1\text{cm}$  (62%), diagnosed at stage I-II (55%). Post-operative plasmas miR-21 expression were found to be 2.1 times increased compared to pre-operative plasmas miR-21 but they were not statistically significant ( $p = 0.063$ ). When categorized according to clinicopathological status, it appears that there is significant difference in miR-21 before and after surgery in the age category  $< 50$  years (increased 1.19 times), stage I-II (decreased 2.18 times), tumor residue  $< 1\text{cm}$  (increased 2.85 times), pre-operative CA-125 levels  $\geq 500 \text{ U/ml}$  (increased 3.29 times) and parity  $\geq 1$  (increased 2.99 times). Up-regulation of post-operative plasmas MiR-21 were associated with a worse prognosis, higher risk of death and lower probability of survival but not

statistically significant (HR = 1.410; p = 0.6254; CI = 0.3510–5.667). In addition, histopathological type II and advanced clinical stages also show a poor prognosis for survival. However, after multivariate analysis with cox regression, it appears that histopathological type II, advanced stage, tumor residue > 1cm and up-regulation of miR-21 post-operative are not independent prognosis markers on survival of epithelial ovarian cancer patients.

**CONCLUSION:** Post-operative miR-21 expression increased by 2.1 times compared to pre-operative but the increase was not significant. While up-regulation of miR-21 post-operative is associated with a greater risk of death and a worse prognosis, therefore miR-21 still has the potential to predict the prognosis of patients with epithelial ovarian cancer.

**KEYWORDS:** MicroRNA-21, miR-21, MiRNA-21, pre-operative, post-operative, clinicopathology, prognosis, survival, epithelial ovarian cancer.