# Common inflammatory biomarkers of cancer prognosis

Bo Angela Wan<sup>1</sup>, MD(C), Michael Lam<sup>1</sup>, BMSc(C), Anthony Furfari<sup>1</sup>, MD(C), Rachel McDonald<sup>1</sup>, MD(C), Leigha Rowbottom<sup>1</sup>, MD(C), Stephanie Chan<sup>1</sup>, BSc(C), Pearl Zaki<sup>1</sup>, BSc(C), Carlo DeAngelis<sup>1,2</sup>, PharmD, Ronald Chow<sup>1</sup>, BMSc(C), George S Charames<sup>3,4,5</sup>, PhD, Henry Lam<sup>1</sup>, MLS, Edward Chow<sup>1</sup>, MBBS and Azar Azad<sup>4</sup>, PhD



<sup>1</sup>Odette Cancer Centre, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, <sup>2</sup>Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, <sup>3</sup>Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, <sup>4</sup>Laboratory Medicine and Pathobiology, University of Toronto, Toronto, <sup>5</sup>Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, <sup>6</sup>Mount Sinai Services Inc., Toronto



# Introduction

- Biomarkers have the potential to act as important tools in predicting prognosis of cancer
- Blood is one of the most readily available sources of biomarkers. In addition to being easy to obtain, levels of the protein and cell constituents in blood provide valuable information regarding the degree of inflammation.
- Inflammatory proteins, leukocyte levels, and platelet levels may be able to predict survival in many

# **Objective**

To summarize the currently available literature reporting on common inflammatory blood biomarkers, excluding cytokines and chemokines, and their association with prognosis in cancer patients.

#### Methods

- A literature search was conducted on Medline and Embase utilizing keywords such as 'neoplasm,' 'inflammation,' 'biomarker,' 'allele,' and 'genomics.'
- Articles that reported on the levels of commonly implemented prognostic biomarkers (Creactive protein (CRP), albumin, white blood cell and platelet counts) and their derivative scores or ratios relating to prognosis were selected for inclusion.
- Information regarding the patient population, cancer type, interventions received, type of biomarker, and the impact on prognosis was extracted

# Results

- Using our search strategy, a total of 3,287 original articles were identified using Medline, and 2,193 using Embase.
- After screening for inclusion and exclusion criteria, 23 studies were included (study sample sizes 62 to 1,825), spanning 11 distinct cancer types
- Prognosis was classified into five different types with overall survival (OS) being the most prevalent (n=18) (5, 8, 10-30). Other outcomes included cancer specific survival (CSS, n=6), disease free survival (DFS, n=6), progression free survival (PFS, n=1), and distant metastasis free survival (DMFS, n=1)
- Prognostic inflammatory blood biomarkers were classified as protein-based (n=21), cell-based (n=13), or both (n=1)

#### Studies that assessed CRP or albumin inflammatory blood biomarkers

- Albumin associated with poor OS (n=6), DFS (n=1), or PFS (n=1) from 6 studies
- CRP were associated with poor OS (n=8), CSS (n=3), DFS (n=3), PFS (n=1), or DMFS (n=1) from 11 studies
- High GPS score (high CRP, low albumin) associated with poor outcome from 7 studies
- High modified GPS score associated with poor outcome from 10 studies
- High CRP/albumin ratio associated with poor outcome from 2 studies

#### Studies that assessed counts and ratios of platelets and leukocytes with outcome in cancer

- Absolute neutrophil count (ANC): High cell count associated with poor outcome in 3
- Absolute monocyte count (AMC): High cell count associated with poor outcome in 1
- White blood cell count (WBC): High cell count generally associated with poor outcome in 2 studies
- Neutrophil-Lymphocyte ratio (NLR): High ratio (high neutrophils, low lymphocytes) associated with poor outcome in 12 studies
- Platelet-Lymphocyte ratio (PLR): high ratio (high platelets, low lymphocytes) generally associated with poor outcome in 4 studies
- Lymphocyte-Monocyte ratio (LMR): Low ratio (high lymphocytes, low monocytes) generally associated with poor outcome in 2 studies

# **Discussion**

- The abundance of literature that found significant associations between inflammatory blood biomarkers and prognosis in cancer patients supported the role of inflammation as an important factor in cancer outcomes.
- Of the leukocyte and platelet measures, the NLR ratio was the most often used prognostic tool and was found to be associated with outcome of at least six cancer
- Measurements of just two blood proteins, CRP and Albumin, could be used to assess prognosis in at least eight cancer types using four different methods of evaluation: protein concentrations taken at face value, and three versions of GPS scoring (GPS, mGPS, new-mGPS).

# Selected references

- Zhang WW, Liu KJ, Hu GL, Liang WJ. Preoperative platelet/lymphocyte ratio is a superior prognostic factor compared to other systemic inflammatory response markers in ovarian cancer patients. Tumour Biol 2015;36(11):8831–7.
  Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, et al. The C-reactive protein/albumin ratio, a novel inflammation-based prognostic score, predicts outcomes in patients with hepatocellular carcinoma. Ann Surg Oncol 2014;22(3):803–10. Martin HL, Ohara K, Kiberu A, Van Hagen T, Davidson A, Khattak MA. Prognostic value of systemic inflammation-based markers in advanced pancreatic cancer. Intern Med J 2014;44(7):676–82. Kinoshita A, Onoda H, Imai N, Iwaku A, Oishi M, Tanaka K, et al. The Glasgow Prognostic Score, an inflammation based prognostic score, predicts survival in patients with hepatocellular carcinoma. BMC Cancer 2013;13:52.
  Wang DS, Ren C, Qiu MZ, Luo HY, Wang ZQ, Zhang DS, et al. Comparison of the prognostic value of various preoperative
- Comparison of the prognostic value of various preoperative inflammation-based factors in patients with stage III gastric cancer. Tumor Biol 2012;33(3):749–56. Jiang X, Hiki N, Nunobe S, Kumagai K, Kubota T, Aikou S, et al. Prognostic importance of the inflammation-based Glasgow
- prognostic score in patients with gastric cancer. Br J Cancer 2012;107(2):275–9.

- [Deng Q, He B, Liu X, Yue J, Ying H, Pan Y, et al. Prognostic value of preoperative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model. J Transl Med 2015;13:66.

  [Na GH, Kim DG, Han JH, Kim EY, Lee SH, Hong TH, et al. Inflammatory markers as selection criteria of hepatocellular carcinoma in living-donor liver transplantation. World J Gastroenterol 2014;20(2);16594–601.

  [Szkandera J, Gerger A, Liegl-Atzwanger B, Absenger G, Stotz M, Samonigg H, et al. Validation of the prognostic relevance of plasma C-reactive protein levels in soft-tissue sarcoma patients. Br J Cancer 2013;109(9):2316–22.

  Xia WX, Zhang HB, Shi JL, Lu X, Wang L, Ye YF, et al. A prognostic model predicts the risk of distant metastasis and death for patients with nasopharyngeal carcinoma based on pre-treatment serum C-reactive protein and N-classification. Eur J Cancer 2013;409):2152–60.

  [Canna K, McMillian DC, McKee RF, McNicol A-M, Horgan PG, McArdle CS. Evaluation of a cumulative prognostic score based on the systemic inflammatory response in patients undergoing potentially curative surgery for colorectal cancer. Br J Cancer 2004;90(9):1707–9.

  Shibutani M, Maeda K, Nagahara H, Ohtani H, Iseki Y, Ikeya T, et al. The prognostic significance of a postoperative systemic inflammatory response in patients with colorectal cancer. World J Surg Oncol 2015;13:194.

  Xu XL, Yu HQ, Hu W, Song Q, Mao WM. A novel inflammation-based prognostic score, the c-reactive protein/albumin ratio predicts the prognosis of patients with operable esophageal squamous cell carcinoma. PLoS One 2015;10(9):e0138657.

# Conclusion

- These prognostic blood biomarkers are not only simple and economical to test for, but also provide prognostic information on duration of expected survival.
- This information is invaluable for patients, family members, and healthcare practitioners in order to help them prepare and plan for the future, such as switching from treatment to supportive or palliative