

# Serum Gamma Glutamyl Transferase (GGT) as a Potential Prognostic Biomarker for Detrimental Neutrophils in Hepatocellular Carcinoma (HCC)

Marcello M Kadharusman (200769932)<sup>1</sup>, Misti McCain<sup>1</sup>, Ruchi Shukla<sup>2</sup>, Helen L Reeves<sup>1</sup>

1. Clinical and Translational Research Institute, Newcastle University, Newcastle upon Tyne, UK

2. Biosciences Institute, Newcastle University, Newcastle upon Tyne, UK

m.m.kadharusman2@Newcastle.ac.uk



## INTRODUCTION

- Incidence and mortality from HCC in the UK have risen faster than any other cancers due to increasing alcohol consumption and prevalence of metabolic disorder.<sup>1</sup>
- Although immune checkpoint inhibitors have been successful in treating various types of cancer, only a small percentage of patients with HCC have responded to it.<sup>2</sup>
- Recent study showed that elevated peripheral neutrophil is associated with poor prognosis, but discovering its mechanism and clinical biomarker of detrimental tumour associated neutrophils (TANs) are still needed to develop new therapies.<sup>3</sup>
- GGT is a membrane-bound enzyme that promotes intracellular glutathione, thus limiting cellular damage.<sup>4</sup> Since GGT has been shown to have a role in tumour progression, serum GGT may be a clinically relevant biomarker of detrimental neutrophils.

## AIMS

- To investigate the potential role of serum GGT as a prognostic biomarker in HCC.
- To explore the relationship between serum GGT and TANs.
- To explore the association between serum GGT and TANs relative to HCC progression.

## METHODS

### HCC Cohort (n=300)

- Freeman Hospital (2000 – 2017)
- Minimum follow-up period of 3 years

### Inclusion Criteria:

- Absence of any organ failure
- Peripheral blood test collected prior to treatment

### Exclusion Criteria

- Coexisting tumour in another organ
- Previously underwent chemotherapy or radiation therapy

### Control Cohort (n=20)

- Undergoing liver disease surveillance

Figure 1. Flowchart of Research Methodology

## RESULTS

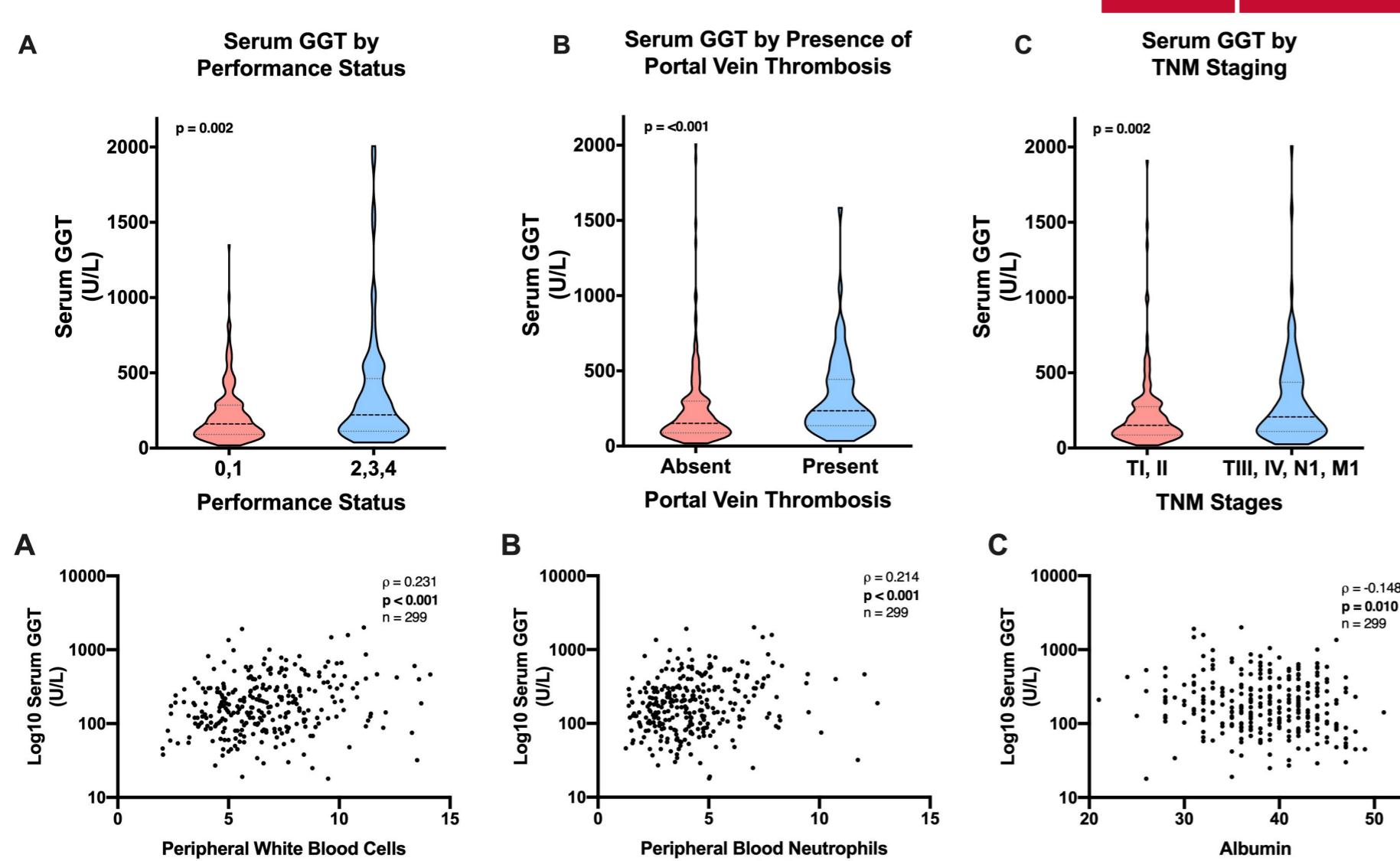


Figure 2. Association between Serum GGT with Clinicopathological Factor.

- Serum GGT was significantly **positively associated** with deteriorating ECOG performance status (A), presence of portal vein thrombosis (B), and advancing TNM stage (C).

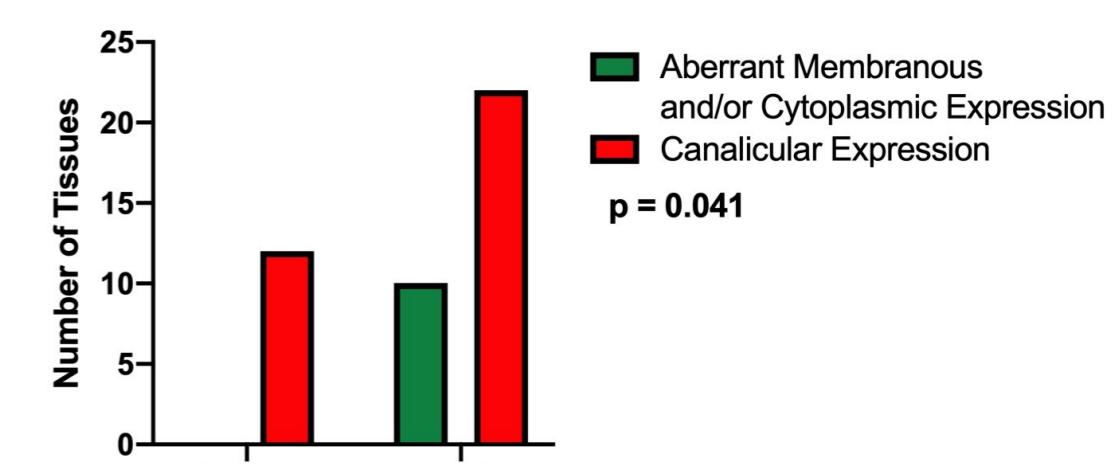


Figure 4. Changes in GGT Expression in the Liver Tissue of Patients with HCC.

- A higher proportion of liver tissues from patients with HCC displayed **aberrant cytoplasmic or membranous GGT expression** compared to the control.

## RESULTS

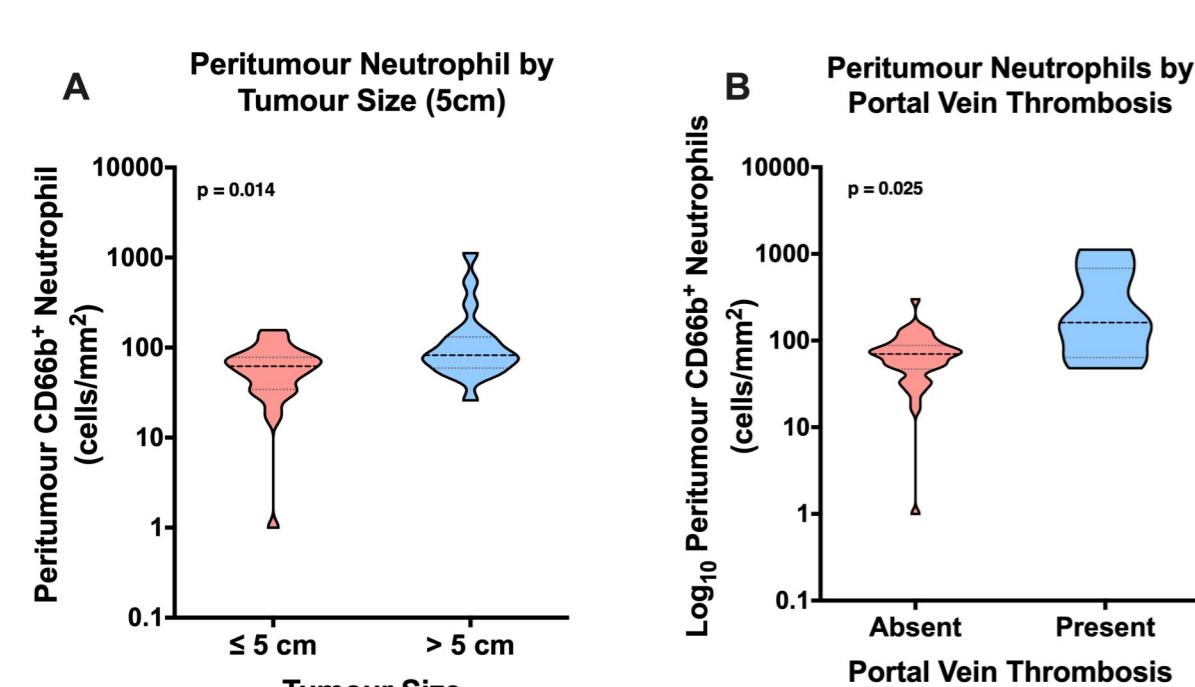


Figure 5. Association between Peritumour CD66b+ Neutrophil Density with Clinicopathological Factor.

- Peritumour neutrophil density was significantly **positively associated** with large tumour (A) and presence of portal vein thrombosis (B).

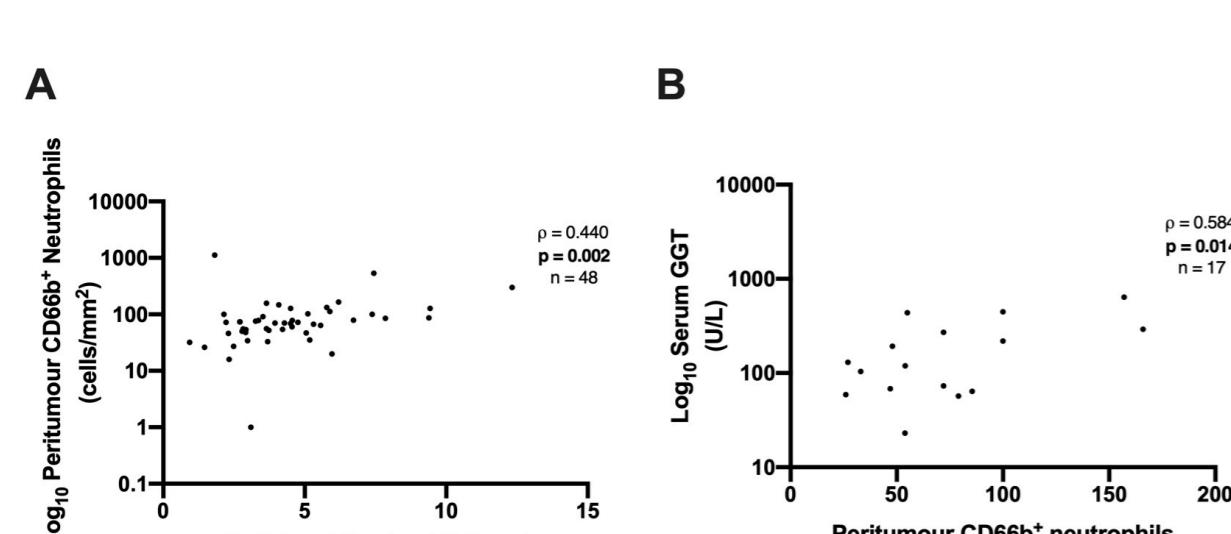


Figure 6. Correlation between Peritumour CD66b+ Neutrophil Density and Level of Peripheral Neutrophil and Serum GGT.

- Peritumour neutrophil density was significantly **positively correlated** with the level of peripheral neutrophil (A) and serum GGT (B).

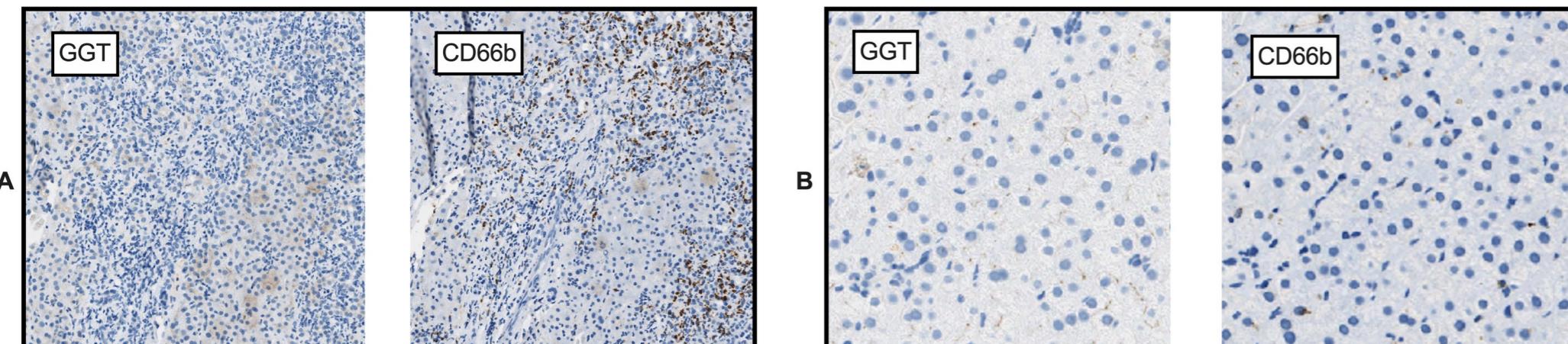


Figure 7. Association between CD66b+ Neutrophils and GGT in Peritumour Area of HCC Tissue.

- Aberrant GGT cytoplasmic staining in the peritumour area of HCC tissue was associated with high density of CD66b+ neutrophils (A).
- Absence of GGT cytoplasmic staining was associated with low density neutrophils (B).

## RESULTS

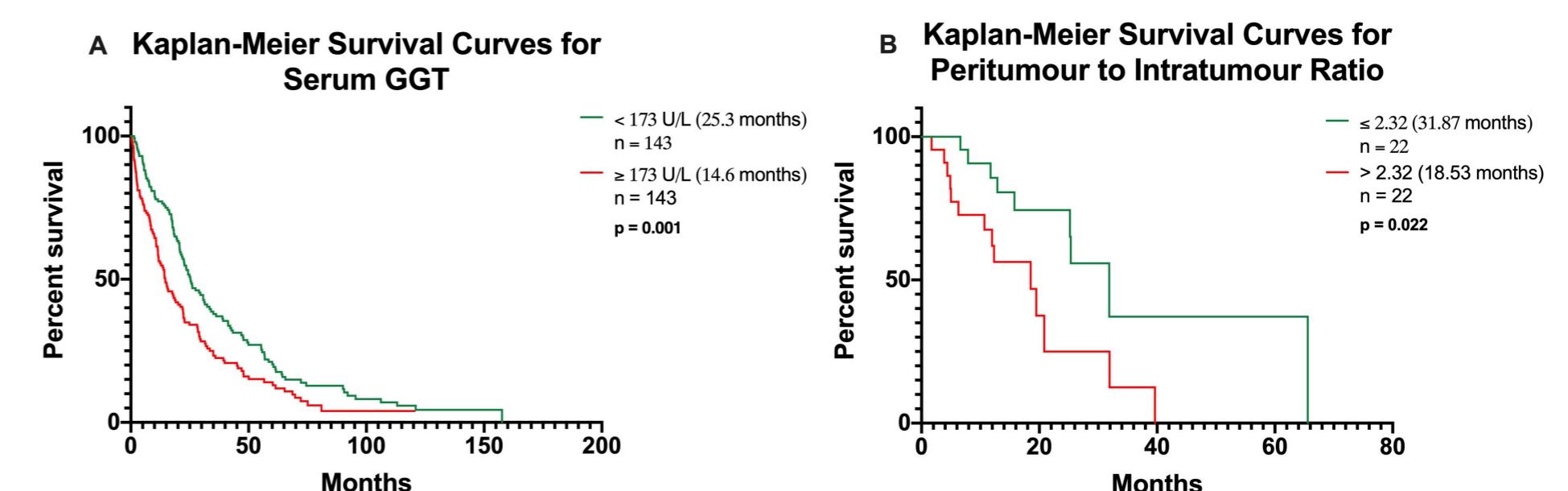


Figure 8. Serum GGT (A) and Peritumour to Intratumour Neutrophil Ratio (B) Association with OS.

Table 1. Multivariate Analysis of Factors Associated with Overall Survival.

Variable	Hazard Ratio (95% CI)	p-value
Serum GGT (> 173 U/L)	1.524 (1.150-2.019)	0.003
PT/IT CD66b+ Neutrophil ratio (> 2.32)	2.922 (1.013-8.426)	0.047

## CONCLUSION & FUTURE WORK

### Conclusion:

- Serum GGT is significantly associated with advanced HCC, deteriorating performance status, and increased circulating peripheral neutrophil.
- In the peritumour area of HCC tissue, aberrant cytoplasmic GGT expression is associated with high density CD66b+ neutrophils.
- Elevated serum GGT and high peritumour to intratumour CD66b+ neutrophil ratio are independent poor prognostic factors in patients with HCC.

### Future work:

- Validate the findings using a larger sample size of liver biopsy tissue.
- Explore serum GGT as a predictive biomarker to guide immunotherapy.
- Explore the combination of pro-tumour neutrophils and T cells as a prognostic and predictive biomarker.

