Survival Analysis of Diabetic Colorectal Cancer Patients On Metformin in Brunei Darussalam

Alex Brandon Wong
PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam
Ravi Patnaik
The Brunei Cancer Centre, Pantai Jerudong Specialist Centre
Li Ling Chaw
PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam
Shir Kiong Lu
The Brunei Cancer Centre, Pantai Jerudong Specialist Centre
Ya Chee Lim (yachee.lim@ubd.edu.bn)
PAPRSB Institute of Health Sciences, Universiti Brunei Darussalam

Research Article

Keywords: Colorectal, Cancer, Metformin, Diabetes, Prognosis, Survival, Stage, Incidence, Association, Hyperglycemic.

Posted Date: April 18th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2749381/v1

Abstract

Metformin, an antihyperglycemic drug, has been associated with antineoplastic effects and could potentially improve colorectal cancer prognosis. There are several conflicting data with regards to the association between metformin use and CRC survival. This study aims to provide more information on the subject while addressing certain limitations. The study was a retrospective cohort study that included colorectal cancer patients from the only cancer centre in the country, The Brunei Cancer Center (TBCC), treated between July 2014 and July 2019. Kaplan-Meier and multivariate Cox proportional hazard regression models were used to analyze the data, construct survival curves and adjust for comorbidities. Of a total of 112 diabetic patients, 79 patients (70.5%) were on metformin and 33 patients (29.5%) were on other anti-hyperglycemic medications. An association between metformin use and lower incidence of stage IV colorectal cancer ($p = 0.046$) was observed, but no significant difference between the metformin group and the non-metformin group in terms of survival probability (log rank $p = 0.13$) was shown. Analysis using multivariate models showed that metformin reduces the hazard ratio by 31.2%, although, this value is statistically insignificant (HR, 0.688; 95% CI 0.286 – 1.654; $p = 0.403$). Among the diabetic colorectal cancer patients, there was no association between survival and metformin therapy. This data reflects the correlation of metformin use and CRC survival within the nation for all CRC diabetic patients diagnosed between July 2014 and July 2019. However, for further extrapolation of data, the association between cancer progression and metformin use requires further investigation and high-powered clinical trials are needed to support these findings.

Background

Globocan 2020 recorded 19.3 million cases of cancer with nearly 10.0 million cancer deaths. Colorectal cancer (CRC) is the third most commonly diagnosed cancer (10.0%) and is the second most common cause of cancer-related deaths (9.4%) in both sexes (1). In the context of Brunei Darussalam, increasing CRC cases with lower survival rates places a heavy burden on the medical resources of the country, attributing to 18.3% of cancer-related mortality, with 6.4% of it being localized to the colon and 11.9% of it being localized to the rectum and anus (2, 3).

Diabetes has been shown to be associated with an increased risk of CRC (4, 5). This relationship has been highlighted as one of the potential comorbidities that should be considered due to shared risk factors (old age, obesity, and inactivity) between diabetes and CRC (6). While this notion seems likely, a meta-analysis noted that there was still a positive association between CRC and diabetes, despite controlling for risk factors (7). Thus, the study demonstrated that shared risk factors played little to no role in CRC incidence. This association is more likely attributed to hormonal and metabolic changes in diabetic patients, promoting the microenvironment for tumor formation and progression, leading to cancer development (8). A meta-analysis on the relationship between diabetes and CRC has elucidated that diabetes further decreases the life expectancy of those with CRC by about 5 years and overall survival is decreased by 18% (9).

Metformin, the first line oral drug given to type 2 diabetic patients, has been reported by several studies to improve the CRC survival rates as well as reducing the risk for CRC among diabetic patients (10–12). Metformin is an oral hypoglycemic drug that falls into the biguanide family of drugs and is commonly used in obese type 2 diabetic patients (13). In addition to modulating molecular targets within the autophagy, cell cycle, apoptosis and inflammation pathways (14), metformin accumulates within mitochondria and inhibits complex I of the electron transport chain. This affects ATP production and causes an increase in the ADP:ATP and AMP:ATP ratio, which in turn leads to the inhibition of gluconeogenesis due to the inhibition of fructose-1,6-bisphosphatase. Moreover, adenosine monophosphate activated protein kinase (AMPK) is activated as a result of the increased ratios and this further impairs the hepatic glucose production while also increasing the uptake of glucose into adipose and muscle cells through GLUT-4 channels (15, 16).

Metformin has also been associated with enhancement of other anti-cancer medications and chemotherapy (17). These antineoplastic effects of metformin are largely due to the inhibition of the mammalian target of rapamycin complex 1 (mTORC1) pathway as well as the activation of the Liver Kinase B1 (LKB1)-AMPK pathways (18). LKB1 has been identified as one of the kinases that phosphorylates and activates AMPK following energy stress. During carcinogenesis, LKB1 has been observed to be inactivated. The activation of this pathway is vital to control and inhibit the mTOR pathway which comprises of two distinct complexes, mTORC1 and mTORC2. mTORC1 is the more relevant complex as it regulates the translation of growth factors including cyclin D1, hypoxia inducible factor 1a and c-myc (19). Thus, the energy stress brought on by metformin causes the upregulation of the LKB1-AMPK pathway that in turn, inhibits the mTORC1 complex. This inhibits processes including cell growth, angiogenesis and the progression of the cell cycle which affects tumorigenesis.

Several similar studies have been conducted with conflicting results. While most studies have demonstrated and concluded that metformin has clear impacts on the survival rates of diabetic CRC patients, few studies have shown no association between metformin use and CRC risk and survival (20–22). However, these studies had their own limitations. For example, in Kowall (2015)’s study, there was no significant association between risk and metformin therapy. However, lifestyle variables like smoking and physical activity were not adjusted for due to lack of the availability of such information, leading to potential confounding factors (21). Thus, this study aims to provide supporting information and clarification regarding metformin’s effect on survival outcomes when analyzed against confounding factors in type 2 diabetic CRC patients based in Brunei Darussalam. In this study, we aim to compare survival outcomes between metformin use and colorectal cancer mortality using Kaplan-Meier test and multivariate Cox proportional hazard regression models to eliminate potential confounding.

Methodology

STUDY DESIGN POPULATION

The study was a retrospective cohort study, whereby data from patient records in the sole national cancer treatment hospital in Brunei Darussalam, The Brunei Cancer Center (TBCC), Pantai Jerudong Specialist Centre, were collected and analyzed to determine the relationship between metformin therapy and mortality.

POPULATION AND SAMPLE

The cases comprised of CRC patients who presented to TBCC between July 2014 and July 2019. Information from all diabetic CRC patients were collected and included in this study. Patients without diabetes, patients with histologies other than colorectal adenocarcinoma and patients with carcinoma *in situ* were excluded. All eligible cases were collected and sampling was not done. The records of a total of 480 CRC patients were available, of which 114 patients were diabetic.

DATA COLLECTION

The data collected includes patient demographics and clinical findings (age and date of diagnosis, gender, race, smoking status, height, weight, BMI, stage of cancer, metformin usage, other specific treatments for diabetes and cancer, use of aspirin, HBA1c levels, presence of comorbidities, as well as overall survival status). The treatment and management of diabetes included the use of medications in the form of gliclazide, sitagliptin, tolbutamide, linagliptin and acarbose and the treatment of cancer was delineated through either surgery, chemotherapy or radiotherapy. The survival outcome of patients was determined by date of death as recorded in patient files at TBCC. Patient's survival status was last checked during February 2020.

A staging calculator (Integrated Cancer Research "TNM Cancer Staging Calculator) was used to generate an overall TNM staging. Comorbidities were numericized using the Charlson Comorbidity Index (CCI) which takes into consideration factors such as age, HBA1c levels, history of heart failure, chronic kidney disease as well as other medical conditions associated with mortality.

DATA ANALYSIS

With regards to sociodemographic analysis, categorical data was compared using the Chi-squared test and Fisher's exact test. Quantitative data was evaluated using the independent t-test. The analysis of data was done with particular focus on estimating the effect of metformin usage on survival statistics. Kaplan-Meier analysis was used to investigate the survival outcomes of single variables and a logrank test was used to compare between the survival curves that were generated. Overall mortality, taking into consideration the various lifestyle, medical and demographic factors including age at diagnosis, stage, BMI and comorbidities were analyzed with a multivariate Cox proportional hazard regression model. Assumption checking for this model was done, including residuals and multicollinearity checking. All tests were two-sided and a p value of less than 0.05 indicated significant findings. Data analysis was performed using the "RStudio Version 1.2.5033" software (23).

Results

DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

Initially, 114 diabetic CRC patients were identified. Two patients were excluded due to unavailable and insufficient information, leading to a total of 112 observations. Patient demographics and clinical characteristics based on their metformin status are summarized in Table 1. The predominantly Malay population (79.5%) comprised of 79 diabetic patients on metformin (70.5%) and 33 patients who were on anti-hyperglycemic medications other than metformin (29.5%). The mean age of patients was 61 years old, with the youngest patient being 29 years old and the oldest being 85 years old. The group of patients who were on metformin therapy were younger than the group of patients who were on other therapies when comparing the mean age of both groups.

Table 1
Demographics of diabetic colorectal cancer patients by metformin treatment status

Variable	Total Population n (%)	Metformin n (%)	Non-Metformin n (%)	p-value
Age at diagnosis	61.0 (10.6) †	60.0 (11.0) †	63.6 (9.1) †	0.101
Age at death	64 (11.3) †	62.9 (11.6) †	65.7 (11.0) †	0.491
Sex	60 (53.6%)	41 (51.9%)	19 (57.6%)	0.852
Male	52 (46.4%)	38 (48.1%)	14 (42.4%)	
Female				
Race	89 (79.5%)	60 (75.9%)	29 (87.9%)	0.243
Malay	18 (16.1%)	15 (19%)	3 (9.1%)	
Chinese	5 (4.4%)	4 (5.1%)	1 (3.0%)	
Others				
Stage	13 (10.9%)	7 (9.0%)	6 (15.6%)	**0.046***
1	35 (31.7%)	24 (30.8%)	11 (34.4%)	
2	44 (39.1%)	37 (46.2%)	7 (21.9%)	
3	20 (18.2%)	11 (14.1%)	9 (28.1%)	
4				
Smoking Status	11 (10.3%)	5 (6.7%)	6 (18.8%)	0.057
Smoker	88 (82.2%)	66 (88.0%)	22 (68.8%)	
Non-Smoker	8 (7.5%)	4 (5.3%)	4 (12.5%)	
Ex-Smoker				
Body Mass Index	25.1 (4.8) †	25.5 (5.2) †	24.3 (3.8) †	0.258
HbA1C	7.3% (1.9%) †	7.2% (1.8%) †	7.4% (2.1%) †	0.566

† mean (Standard Deviation)

* $p < 0.05$

Variable	Total Population	Metformin	Non-Metformin	p-value
	n (%)	n (%)	n (%)	
Cancer treatments	87 (79.1%)	63 (80.8%)	24 (72.7%)	0.499
Chemotherapy, Yes	21 (18.9%)	13 (15.4%)	8 (25.0%)	0.298
Radiotherapy, Yes	63 (56.8%)	46 (59.0%)	17 (51.5%)	0.623
Surgery, Yes				
† mean (Standard Deviation)				
* $p < 0.05$				

USE OF METFORMIN AND SURVIVAL

Among the 112 patients, 80 patients (71.4%) were still alive as of the time of last follow up and 32 patients (28.6%) were reported to be deceased. The group on metformin therapy showed better survival statistics compared to the group without metformin. In the metformin group, there were 60 patients alive (75.9%) and 19 deaths (24.1%) while the non-metformin group had 20 patients still alive (60.6%) and 13 deaths (39.4%). Figure 1 shows the survival curves of these two groups. Although not statistically significant (P-value = 0.13), visual inspection shows that the group not on metformin therapy was associated with a lower chance of survival compared to the group on metformin therapy.

The findings of the multivariate cox proportional hazards regression model are summarized in Table 2. Multivariate analysis has also shown relatively similar results (p-value > 0.05) despite adjustments of different variables that may affect mortality such as age at diagnosis, stage, BMI and comorbidities. The analysis shows that after adjustment, metformin reduces the death hazard ratio by a factor of 0.688 or 31.2%. However, this value is statistically insignificant (HR, 0.688; 95% CI 0.286–1.654; p = 0.403).

Table 2
Showing adjusted hazard ratios after taking the comorbidities into consideration

Variable	Regression Coefficient	Hazard Ratio (95% CI)	p-value
Metformin Used	− 0.374	0.688 (0.286, 1.653)	0.403
Age at diagnosis	0.006	1.007 (0.994, 0.959)	0.791
Stage	0.000	1.000	0.273
1	− 1.115	0.328 (0.045, 2.407)	0.316
2	0.786	2.196 (0.472, 10.205)	0.141
3	1.509	4.522 (0.607, 33.714)	
4			
BMI	− 0.253	0.776 (0.467, 1.292)	0.330
Charlson Comorbidity Index	− 0.007	0.993 (0.717, 1.374)	0.964

Discussion

Overall, the findings of this study showed no significant association between metformin and all-cause mortality in diabetic CRC patients, even after adjusting for confounding factors using multivariate analysis. While the survival curves show that metformin patients have a higher survival probability compared to those not on metformin, this association is not statistically significant. These findings are similar to the findings of a study conducted by McMenamin (2016) which boasted several strengths including a large sample size, completeness of data allowing more detailed analyses as well as adjustments to prevent immortal time bias (22). Other studies have also shown that metformin is not associated with colorectal cancer risk and has no impact on disease free and progression free survival (24, 25).

While there was no significant association between metformin use and mortality in diabetic CRC patients, there are multiple aspects of this study that are worth noting. From Table 1, in terms of cancer stage, the group on metformin therapy appears to be suffering from more advanced stages of cancer (60.3%) compared to the group not on metformin therapy (50.0%). Despite this, the survival curves still show that metformin increases the probability of survival in these patients. In addition to that, compared to previous studies that have been conducted on this subject, the reduction in hazard ratio in this study is rather high. We found a 31.2% reduction in the hazard ratio, whereas in Paulus' (2016) study, there was a significant reduction in the hazard ratio by 13.0% (4). The fact that this study was a population study and did not do sampling should also be a factor that should not be overlooked.

One significant finding, however, was the association between metformin use and the reduced incidence of metastatic CRC. This may point towards the notion that metformin therapy helps to improve prognosis by inhibiting the progression of cancer to a metastatic state contrary to the idea that metformin therapy has direct impacts on CRC mortality. Kang's (2018) research on the anti-metastatic effects of metformin through repression of IL-6 induced epithelial mesenchymal transition (EMT) demonstrates this notion. IL-6 is a cytokine that is vital in mediating inflammation and immune responses, as well as mediating the tumor promoting effects of inflammation related conditions by inducing EMT. EMT in turn, promotes the migration and invasion of cancer cells and initiates metastasis. The study had found that through genomic data analysis, there is reduced IL-6 signaling epithelial mesenchymal transitioning (26).

There are noteworthy strengths and limitations in this study. Firstly, due to the availability of extensive and detailed records found in the national healthcare information system, information about comorbidities were recorded comprehensively. Within this database, detailed test results reflecting the severity and control of the diabetes were also easily accessible. This was important as the severity of the diabetes could well prove to be a potentially strong time-varying confounder. Moreover, the survival status of all patients were analyzed and there was no single patient that was lost to follow up. As for the limitations, this data may not truly mirror the antineoplastic effects of metformin due to the small population of the country. One further weakness was the failure to obtain data on the duration of metformin exposure including metformin dosing, to determine the dose-response relationship between the drug and the outcome. Moreover, the findings of this study may have been attributed to immortal time bias as the drug exposure was not treated as time dependent. The lack of previous information on each diabetic case is also lacking. These patients may already have high blood glucose level for prolonged periods may had longer history of diabetes and inflammation, thereby affecting CRC survival. In addition, other treatments of diabetes, such as insulin injections or glucagon-like peptide 1 may play a role in CRC survival, which is not reported in this case. Another plausible confounding factor is exclusion of patients that could not take metformin due to renal function failure. Lastly, this study only examines the impact of metformin on all-cause mortality and may not be reflective of cancer related mortality as information about the specific cause of mortality was not readily available. However, the study was able to control for the potential confounding by adjusting for glycemic control (HBA1c), age, body mass index and other comorbidities.

Conclusion

Although many studies have tried to demonstrate the antitumor effects of metformin, the results have not been conclusive, raising unanswered questions about the antineoplastic effects of metformin. This study adds valuable information, as previous studies have noted an association between colorectal cancer and diabetes. Moreover, metformin is a relatively low risk drug that is very affordable. The evidence provided by this study does not support a significant association between metformin and colorectal cancer mortality. This study has several limitations including a small sample size, immortal time bias, failure to obtain specific information on metformin therapy and all-cause mortality. Given the findings of this study, further studies are warranted investigate the association between cancer progression and metformin

usage. Larger powered trials are needed to further assess the impact of metformin on survival outcomes of colorectal cancer patients.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from PAPRSB Institute of Health Sciences Research Ethics Committee. Informed consent was waived by PAPRSB Institute of Health Sciences Research Ethics Committee with reference number: UBD/PAPRSBIHSREC/2019/31.

Consent for publication

Not applicable

Availability of data and materials

All raw data from this study was available on request from corresponding author

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Funding

This work was funded by Competitive Research Grant of Universiti Brunei Darussalam UBD/OAVCRI/CRGWG(020)/180101.

Authors' contributions

YCL, SKL and RP conceived and designed the study, and supervise the primary researcher. LLC aided in the analysis and interpretation of data. ABW collected the data and wrote the final manuscript. YCL edited the manuscript and all authors approve the final manuscript.

Acknowledgements

We would like to thank the nurses of The Brunei Cancer Centre, Pantai Jerudong Specialist Centre, for kind assistance during data collection, and Universiti Brunei Darussalam for support.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49.
2. Ministry Of Health. Health Information Booklet 2017. 2017.
3. Lee SHF, Abdul Rahman H, Abidin N, Ong SK, Leong E, Naing L. Survival of colorectal cancer patients in Brunei Darussalam: comparison between 2002–09 and 2010–17. BMC Cancer. 2021;21(1):1–15.
4. Paulus JK, Williams CD, Cossor FI, Kelley MJ, Martell RE. Metformin, diabetes, and survival among US veterans with colorectal cancer. Cancer Epidemiol Prev Biomarkers. 2016;25(10):1418–25.
5. Suh S, Kim K-W. Diabetes and cancer: is diabetes causally related to cancer? Diabetes Metab J. 2011;35(3):193–8.
6. Association AD. 3. Foundations of care and comprehensive medical evaluation. Diabetes Care. 2016;39(Supplement 1):S23–35.
7. Yuhara H, Steinmaus C, Cohen SE, Corley DA, Tei Y, Buffler PA. Is diabetes mellitus an independent risk factor for colon cancer and rectal cancer? Am J Gastroenterol. 2011;106(11):1911.
8. Singh RK, Shrinet K, Tripathi A, Chaurasia AK, Kumar A. RISK ESTABLISHED BETWEEN TYPE II DIABETES MELLITUS AND CANCER: A REVIEW. J Sci Res. 2019;63:69–77.
9. Zhu B, Wu X, Wu B, Pei D, Zhang L, Wei L. The relationship between diabetes and colorectal cancer prognosis: a meta-analysis based on the cohort studies. PLoS ONE. 2017;12(4):e0176068.
10. Cheng Y, Chen Y, Zhou C, Shen L, Tu F, Xu J et al. For colorectal cancer patients with type II diabetes, could metformin improve the survival rate? A meta-analysis.Clin Res Hepatol Gastroenterol. 2019
11. Henderson D, Frieson D, Zuber J, Solomon SS. Metformin has positive therapeutic effects in colon cancer and lung cancer. Am J Med Sci. 2017;354(3):246–51.
12. Demb J, Yaseyyedi A, Liu L, Bustamante R, Earles A, Ghosh P et al. Metformin Is Associated With Reduced Odds for Colorectal Cancer Among Persons With Diabetes.Clin Transl Gastroenterol. 2019;10(11).
13. Ritter J, Lewis L, Mant T, Ferro A. A textbook of clinical pharmacology and therapeutics. CRC Press; 2008.
14. Kamarudin MNA, Sarker MMR, Zhou JR, Parhar I. Metformin in colorectal cancer: molecular mechanism, preclinical and clinical aspects.J Exp Clin Cancer Res. 2019;38(1).
15. Rena G, Hardie DG, Pearson ER. The mechanisms of action of metformin. Diabetologia. 2017;60(9):1577–85.

16. Scarpello JHB, Howlett HCS. Metformin therapy and clinical uses. Diabetes Vasc Dis Res. 2008;5(3):157–67.
17. Zhang H-H, Guo X-L. Combinational strategies of metformin and chemotherapy in cancers. Cancer Chemother Pharmacol. 2016 Jul;78(1):13–26.
18. Li M, Li X, Zhang H, Lu Y. Molecular mechanisms of metformin for diabetes and cancer treatment.Front Physiol. 2018;9.
19. Shackelford DB, Shaw RJ. The LKB1–AMPK pathway: metabolism and growth control in tumour suppression. Nat Rev Cancer. 2009;9(8):563–75.
20. Bodmer M, Becker C, Meier C, Jick SS, Meier CR. Cancer Epidemiol Prev Biomarkers. 2012;21(2):280–6.
21. Kowall B, Stang A, Rathmann W, Kostev K. No reduced risk of overall, colorectal, lung, breast, and prostate cancer with metformin therapy in diabetic patients: database analyses from Germany and the UK. Pharmacoepidemiol Drug Saf. 2015;24(8):865–74.
22. Mc Menamin UC, Murray LJ, Hughes CM, Cardwell CR. Metformin use and survival after colorectal cancer: A population-based cohort study. Int J cancer. 2016;138(2):369–79.
23. R Core Team. R: A language and environment for statistical computing. Vienna: R Foundation for Statistical Computing; 2014.
24. Bradley MC, Ferrara A, Achacoso N, Ehrlich SF, Quesenberry CP, Habel LA. A cohort study of metformin and colorectal cancer risk among patients with diabetes mellitus. Cancer Epidemiol Prev Biomarkers. 2018;27(5):525–30.
25. Fransgaard T, Thygesen LC, Gögenur I. Association between metformin use after surgery for colorectal cancer and oncological outcomes: A nationwide register-based study. Int J cancer. 2018;143(1):63–72.
26. Kang S, Kim BR, Kang M-H, Kim D-Y, Lee D-H, Oh SC et al. Anti-metastatic effect of metformin via repression of interleukin 6-induced epithelial–mesenchymal transition in human colon cancer cells.PLoS One. 2018;13(10).

Figures

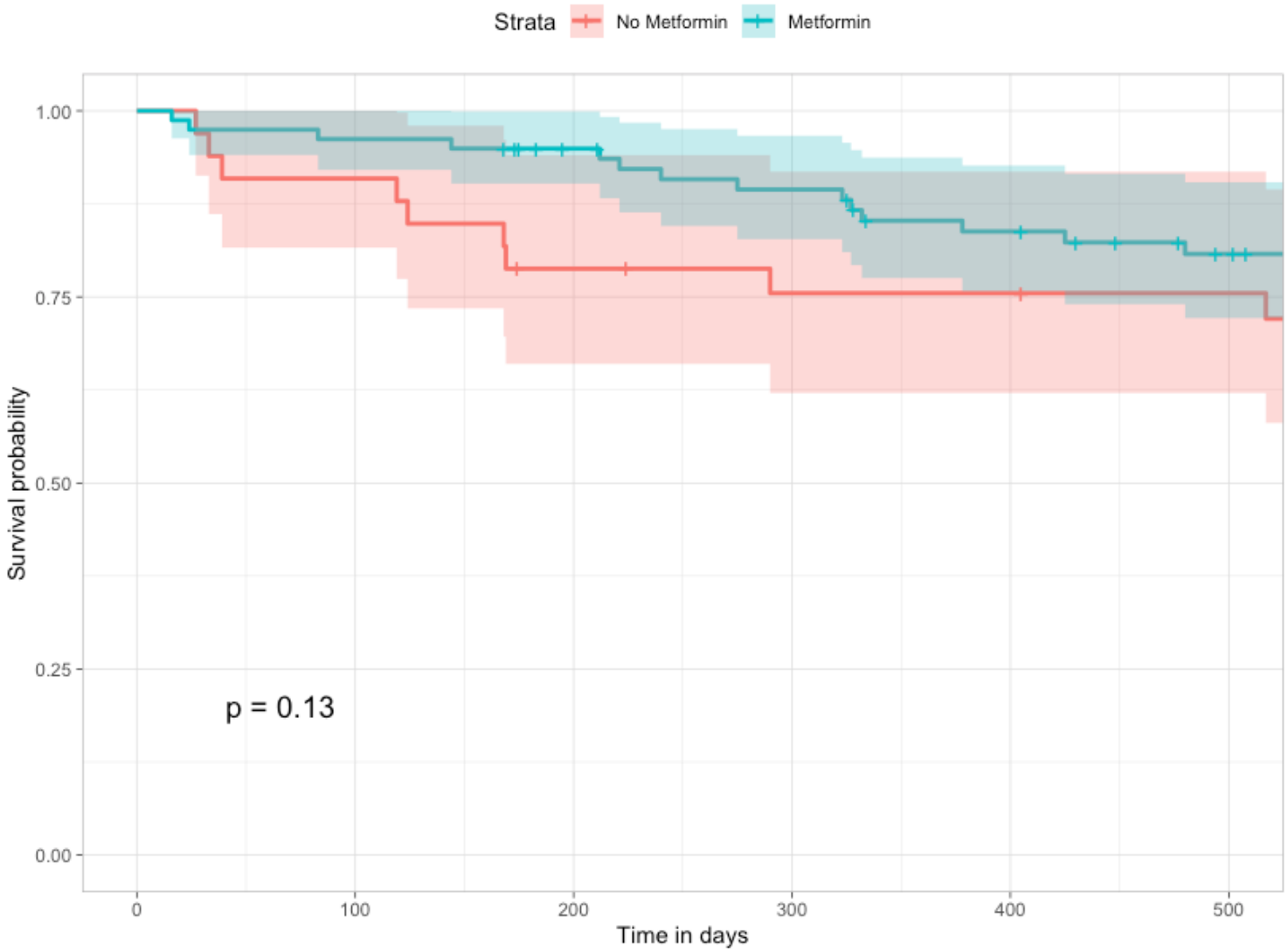

Figure 1

Overall Survival according to metformin use