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Metformin exposure after glioblastoma diagnosis and mortality: A large population-based study

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Abstract

Background. Glioblastoma (GBM) is an aggressive primary brain malignancy with limited therapeutic options and poor survival outcomes. Recent real-world studies and early-phase clinical trials evaluating metformin have yielded mixed findings. This study assessed the association between post-diagnosis metformin exposure and all-cause mortality in a large population-based cohort of older adults with GBM.

Methods. A retrospective cohort study was conducted utilizing the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Adults aged ≥66 years diagnosed with GBM between 2007 and 2018 were included, excluding those with other malignancies or diagnoses made by autopsy or death certificate. Metformin exposure was modeled as a time-varying covariate, defined by the first prescription filled after diagnosis. Cox models with time-dependent covariates estimated adjusted time-varying hazard ratios (HRs) for mortality in the overall cohort and selected subgroups.

Results. Among 16,069 eligible patients, 2,850 (17.7%) were exposed to metformin after diagnosis. Over half (55.8%) died within six months. In the full cohort, metformin exposure was not associated with mortality during the first three months (HR = 1.02; 95% CI: 0.91-1.14) but was linked to increased mortality between 3-9 months (HR = 1.22; 95% CI: 1.10-1.34) and beyond nine months (HR = 1.20; 95% CI: 1.09-1.14). A similar pattern was consistent across subgroup analyses.

Conclusions. In this large cohort of older adults with GBM, metformin exposure after diagnosis was not associated with reduced mortality and was linked to increased mortality beyond the initial three months. These findings underscore the need for prospective studies and randomized controlled trials to clarify metformin's role in GBM outcomes.

Key Points

- Glioblastoma (GBM) is an aggressive brain cancer with poor survival and few treatments
- Metformin shows anticancer activity, but its role in GBM remains uncertain
- In older adults with GBM, metformin exposure was not linked to improved survival

Glioblastoma (GBM) is the most aggressive and lethal primary brain tumor, with a median survival of less than two years despite standard treatment.[1] It disproportionately affects older adults—half of new cases occurring in patients over 64—and is more prevalent in men.[1,2] The current standard of care, which include maximal surgical resection, radiotherapy, and temozolomide chemotherapy, provides only modest survival benefits, and treatment options for recurrent GBM remain poorly defined.[3] The high clinical and economic burden of GBM, driven by intensive treatment requirements and rapid disease progression, underscores the urgent need for novel therapeutic strategies to improve survival outcomes.

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Importance of the Study

Glioblastoma (GBM) is the most aggressive primary brain tumor, with limited treatment options and poor survival outcomes. Identifying therapies that may improve prognosis is therefore of critical importance. Metformin, a widely used antidiabetic drug, has demonstrated anticancer activity in preclinical studies, but evidence in GBM has been inconsistent. This study, leveraging a large, nationally representative cohort of older adults with GBM, provides the most comprehensive evaluation to date of metformin exposure following diagnosis and survival outcomes. We found no evidence of a protective effect and, instead, observed a modest increase in mortality hazards beyond the initial three months of survival. These findings underscore the limitations of observational data, highlight the potential influence of unmeasured metabolic and clinical factors, and point to the need for future studies with greater clinical detail or randomized trial designs to clarify whether metformin has any therapeutic role in GBM.

Metformin, a widely used antidiabetic medication, has demonstrated anticancer properties through mechanisms such as inhibition of tumor proliferation, reduction of insulin-mediated growth signaling, and induction of apoptosis.[4,5,6,7] Both in vitro and in vivo studies have shown that metformin inhibits glioma cell proliferation and invasion, and induces apoptosis.[5,7] These effects appear to be both direct—by targeting tumor cells—and indirect—by reducing circulating glucose and insulin levels.[5,6,7] Notably, metformin has been shown to selectively target brain tumor-initiating cells, a subpopulation of glioma cells thought to contribute to the high resistance of gliomas to standard chemotherapy and to play a key role in tumor recurrence.[5]

Prompted by these promising biological effects, numerous epidemiological studies have examined the association between metformin use and cancer outcomes. Protective effects have been observed in several cancer types, including liver, pancreatic, colorectal, breast,[8] and head/neck cancer.[9] However, findings across studies remain inconsistent, potentially due to variations in study populations and underlying biological mechanisms. In contrast, relatively few studies have investigated the impact of metformin in GBM, and their findings results have been inconclusive.[5,6,10,11]

Given metformin's potential anticancer effects and the ongoing need for improved GBM therapies, this study aimed to evaluate the association between metformin use and all-cause mortality in patients diagnosed with GBM, using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.

Methods

Study Design, Data, and Population

This retrospective cohort study used the SEER database combined with Medicare records.[12] The SEER database encompasses 18 population-based registries throughout the US that regularly gather patient information.[13] The database is composed of linkable de-identified information on cancer incidence, patient demographics, including age at diagnosis, race, gender, year of diagnosis, histology, tumor features, pharmacy data, and all-cause mortality.

The study included only newly diagnosed GBM patients. Patients 66 years and older with a first primary diagnosis of GBM (International Classification of Diseases for Oncology, Third Edition [ICD-O-3] morphology codes 9440-9442, 9445) between January 1, 2007, and December 31, 2018, were identified from the SEER-Medicare linked database and included in the study (see Supplementary Methods). The index date was defined as the date of the first GBM diagnosis. Eligible patients were required to have continuous enrollment in Medicare Part A and B for at least 12 months prior to the index date and enrollment in Medicare Part D on or before the index date. Patients with a history of other primary malignancies or those diagnosed with GBM through autopsy or death certificate only were excluded from the analysis.

Metformin Exposure

Metformin exposure was tracked as a time-dependent covariate in the post-index period. To operationalize this approach, we prepared the dataset for the counting process style of input, whereby each patient's survival period following GBM diagnosis was parsed into 30-day intervals and examined for the first incident metformin prescription, in which case the patient would be classified as exposed beginning in the next 30-day interval until death or censoring. Classifying patients as exposed only after having received a prescription for metformin and processing the data in this way is critically important for avoiding immortal time bias in the outcome modeling described below.[14,15]

Covariates

Baseline medications were recorded during the year prior to index date, including metformin and other medications/classes potentially impacting cancer progression including beta-blockers, non-steroidal anti-inflammatory drugs (NSAIDs), statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), fluoxetine, insulin and other oral antidiabetic medications (i.e., sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, sodium-glucose transport protein 2 inhibitors, alpha-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists, and amylin analogues).

Comorbidities were assessed using sub-scores from the Klabunde modification of the Charlson Comorbidity Index (CCI), with diagnoses identified based on ICD-9 and ICD-10 codes.[16,17] The CCI was calculated using Medicare claims data from the year prior to cancer diagnosis. Primary treatments after GBM diagnosis—including surgery, chemotherapy, and

radiotherapy—were identified through SEER-reported data or Medicare claims (Supplementary Table S1).

Outcome

Mortality from any cause and time to death were assessed using data from the Medicare database. Patients were followed from their data of GBM diagnosis until death, loss to follow-up, or the end of the study period on December 31, 2019, whichever transpired first.

Statistical Analysis

Patient characteristics were summarized by medians with the first and third quartiles for continuous variables and by frequencies with percentages for categorical variables. Characteristics were not shown stratified by metformin exposure because the patients exposed changed over the survival period. Cox regression models were used to evaluate the association between time-dependent metformin exposure after GBM diagnosis and all-cause mortality. Models were adjusted for baseline covariates, including age at diagnosis (years, continuous and mean-centered), sex, race, ethnicity, diabetes (Charlson-defined indicator for diabetes with or without complications), CCI, and prescription medications including fluoxetine, NSAIDs, beta blockers, ACE inhibitors, ARBs, statins, insulin, and other oral antidiabetic medications. Primary cancer treatments (chemotherapy, radiotherapy, or both) and cancer-directed surgery, as recorded in SEER, were also included as covariates. Associations were estimated in terms of hazard ratios (HRs) with 95% confidence intervals. In anticipation that the effect of metformin might change over the course of survival, HRs for metformin exposure were allowed to vary after timepoints corresponding approximately to major treatment decision milestones, specifically at 3 months and 9 months post-diagnosis. Given the substantial heterogeneity in the clinical conditions of patients with GBM and the variability in subsequent treatment patterns, we conducted several exploratory subgroup analyses to assess the consistency of our findings. The results from these sensitivity analyses should be interpreted cautiously, as some were not pre-specified and no formal adjustment for multiplicity was performed. Subgroup analyses were performed in the following cohorts: patients with diabetes, patients receiving surgery with or without other primary treatments, patients treated with both chemotherapy and radiotherapy, patients receiving chemotherapy or both chemotherapy and radiotherapy, patients diagnosed in 2013 or later, and patients newly exposed to metformin after diagnosis. All analyses were performed using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina, USA).

Results

Between 2007 and 2018, a total of 16,069 patients with a GBM diagnosis were identified (Table 1). The median age of the cohort was 74 years (first and third quartiles: [70, 80]), with 52.1% male and the majority identified as white (91.1%). Common baseline comorbidities included cardiovascular disease (32.5%), diabetes (29.2%), chronic obstructive pulmonary disease (20.9%) and obesity (20.3%). The mean CCI was 2.0 (SD = 2.0).

Nearly half of the patients (49.6%) underwent surgical intervention. Cancer-directed therapy was received by 59.3% of the cohort, including 15.9% who received radiotherapy only, 4.8% chemotherapy only, and 38.5% a combination of both. The remaining 40.7% did not receive either modality. Prior to GBM diagnosis, 2,181 (13.6%) of patients had been exposed to metformin. Following diagnosis, 2,850 (17.7%) received metformin during follow-up, among whom 669 (23.5%) were not exposed prior. Mortality was high, with 32.6% of patients dying within 3 months, 55.8% within 6 months, and 76.1% within one year of diagnosis.

In the covariate-adjusted model, metformin exposure following GBM diagnosis was not associated with mortality hazard during the initial three months of survival (HR = 1.02; 95% CI: 0.91-1.14). However, a higher mortality hazard was observed among patients exposed to metformin between three and nine months (HR = 1.22; 95% CI: 1.10–1.34) and beyond nine months after GBM diagnosis (HR = 1.20; 95% CI: 1.09–1.14 (Table 2).

A similar temporal pattern was evident across all subgroup analyses (Table 2). For example, among patients with diabetes (N = 4,684), metformin exposure during the first three months and between three and nine months after diagnosis was not significantly associated with mortality (HR = 0.95; 95% CI: 0.81–1.11 and HR = 1.15; 95% CI: 0.99–1.34, respectively), but elevated hazards emerged beyond nine months (HR = 1.26; 95% CI: 1.07–1.48). Among patients treated with both chemotherapy and radiotherapy (N = 6,185), no statistically significant association was detected during the first three months (HR = 1.07; 95% CI: 0.80–1.42), whereas increased mortality hazards were observed between three and nine months (HR = 1.29; 95% CI: 1.09–1.52), but not beyond nine months (HR = 1.10; 95% CI: 0.95–1.26). Comparable results were seen in the subgroups defined by surgery (with or without other primary treatments), chemotherapy alone or combined with radiotherapy, GBM diagnosis since 2013, and newly exposed to metformin after GBM diagnosis. Complete model results for the overall cohort and all subgroups are presented in Supplementary Tables S2-S8.

Discussion

In this large population-based cohort study of older adults with GBM, exposure to metformin following diagnosis was not associated with reductions in mortality risk. Indeed, metformin exposure was linked to modestly increased mortality hazards after the initial three months of survival, both in the overall cohort and all subgroups we evaluated.

These findings contrast with preclinical studies, which have consistently demonstrated antitumor properties of metformin in glioma models, including inhibition of tumor cell proliferation and invasion, and induction of apoptosis.[4,5,7] Proposed mechanisms—such as direct metabolic interference within tumor cells and indirect effects through reductions in circulating glucose and insulin—have

Table 1. Patient characteristics at GBM diagnosis ($N = 16,069$).

Demographics	
Age (years)	
Median [1st, 3rd quartiles]	74 [70, 80]
Age group, *n* (%)	
66–70	4691 (29.2)
71–75	4279 (26.6)
76–80	3502 (21.8)
≥81	3597 (22.4)
Male, *n* (%)	8364 (52.1)
Race, *n* (%)	
White	14640 (91.1)
Black	779 (4.9)
Asian or Pacific Islander	587 (3.7)
Other/Unknown	63 (0.4)
Hispanic Ethnicity	1596 (9.9)
Year of GBM diagnosis	
2007–2010	3075 (19.1)
2011–2013	3753 (23.4)
2014–2016	4746 (29.5)
2017–2018	3596 (22.4)
Comorbidity *n* (%)	
CCI	
Median [1st, 3rd quartiles, max]	1 [0, 3, 12]
0	4691 (29.2)
1–2	6262 (38.9)
3–4	3314 (20.6)
≥5	1802 (11.2)
Acute MI	369 (2.3)
CVD	5225 (32.5)
CHF	1937 (12.1)
COPD	3265 (20.3)
Dementia	852 (5.3)
Diabetes	4684 (29.2)
History of MI	881 (5.5)
Liver disease	875 (5.5)
Paralysis	2117 (13.2)
PVD	2570 (15.9)
Renal disease	2010 (12.5)
RA	607 (3.8)
Obesity	3357 (20.9)
Treatment after GBM diagnosis, *n* (%)	
Surgery	7995 (49.6)
Radiotherapy	2569 (15.9)
Chemotherapy	774 (4.8)
Radiation and chemotherapy	6185 (38.5)
No radiation or chemotherapy	6541 (40.7)
Drug exposure in year prior to GBM diagnosis, *n* (%)	
NSAIDs	1665 (10.4)
Beta-blockers	5696 (35.5)
ACE inhibitors	4478 (27.9)
ARBs	2780 (17.3)

(Continued)

Table 1. Continued.

Demographics	
Statins	6769 (42.1)
Insulin	2309 (14.4)
Metformin	2181 (13.6)
Other oral antidiabetic medications[a]	1930 (12.1)
Fluoxetine	478 (2.9)

[a]Other oral diabetes medications include: sulfonylureas, meglitinides, thiazolidinediones, dipeptidyl peptidase 4 inhibitors, sodium-glucose transport protein 2 inhibitors, alpha-glucosidase inhibitors, glucagon-like peptide-1 receptor agonists, and amylin analogues.
Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; CCI, Charlson comorbidity index; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; GBM, glioblastoma; MI, myocardial infarction; NSAIDs, non-steroid anti-inflammatory drugs; PVD, peripheral vascular disease; RA, rheumatoid arthritis; SEER, Surveillance, Epidemiology, and End Results.

Table 2. Time-varying mortality hazard ratios associated with time-dependent metformin exposure following GBM diagnosis

	Metformin vs. no metformin exposure					
	During survival months 0-3		During survival months 3-9		After 9 months of survival	
	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Full cohort (*N*=16,069)	1.02	(0.91, 1.14)	1.22	(1.10, 1.34)	1.20	(1.09, 1.32)
Among only the patients with diabetes (*N*=4,684)	0.95	(0.81, 1.11)	1.15	(0.99, 1.34)	1.26	(1.07, 1.48)
Among only the patients receiving surgery with or without other primary treatments (*N*=7,995)	1.05	(0.87, 1.27)	1.22	(1.05, 1.41)	1.10	(0.96, 1.26)
Among only the patients treated with both chemotherapy and radiotherapy (*N*=6,185)	1.07	(0.80, 1.42)	1.29	(1.09, 1.52)	1.10	(0.95, 1.26)
Among only the patients receiving chemotherapy alone or combined with radiotherapy (*N*=6,959)	1.14	(0.88, 1.46)	1.24	(1.07, 1.45)	1.12	(0.98, 1.29)
Among only the patients diagnosed since 2013 (*N*=9,757)	1.03	(0.88, 1.21)	1.16	(1.004, 1.34)	1.07	(0.93, 1.23)
Among only new users (patients without metformin exposure in the year prior to diagnosis, *N*=13,888)	0.94	(0.74, 1.19)	1.22	(1.07, 1.39)	1.21	(1.08, 1.36)

Abbreviations: CI, confidence interval; GBM, glioblastoma.

suggested a potential for improved outcomes.[5,7] However, while epidemiologic studies in other cancers have suggested protective associations,[8,9] evidence specific to GBM remains limited and inconclusive.

Recent real-world studies and early-phase clinical trials on GBM patients exposed to metformin have yielded mixed findings. In a cohort of 1,093 GBM patients with high-grade glioma, reported survival benefits were reported for WHO grade III but not for grade IV gliomas.[5] A retrospective analysis of 988 GBM patients suggested a survival trend benefit favoring metformin use in diabetic patients, although sample size limitations precluded firm conclusions.[11] Another small GBM cohort study suggested prolonged progression-free intervals in metformin users.[10] Conversely, a pooled analysis of three prospective randomized trials reported no survival benefit, although interpretation was constrained by the small number of metformin users.[6] A handful of early-phase clinical trials exploring metformin in combination with standard or investigational therapies in GBM patients have shown inconsistent results.[7] Collectively, the available literature remains sparce, heterogeneous, and largely inconclusive.

Our findings, based on a large, nationally representative cohort, showed no survival benefit associated with metformin exposure after GBM diagnosis and, beyond the initial three months, a modest increase in mortality hazards. Several factors may underlie these findings, including confounding by indication and diabetes severity. Patients prescribed metformin post-diagnosis may represent a subgroup with more severe or poorly controlled diabetes, more adverse metabolic profiles, higher comorbidity burdens, or cancer-associated cachexia—factors associated with worse prognosis.[18–20] Although we accounted for an extensive set of covariates and modeled time-dependent metformin exposure, the potential for residual confounding from unmeasured factors such as glycemic control, functional status, or cancer burden cannot be dismissed.

The observation of increased mortality hazards associated with metformin exposure after having survived with a GBM diagnosis for at least three months in each of the subgroups we evaluated reinforces the concern over latent confounding. This pattern is unlikely to be attributable to the natural course of the disease, as it was evident across all subgroups.

Instead, it may reflect residual ongoing metabolic dysfunction, frailty, or treatment resistance among longer-term survivors—variables not captured in claims data. In this context, the observed associations likely stem from unmeasured systemic deterioration, not metformin's pharmacologic effects. To our knowledge, no preclinical or clinical evidence supports a harmful effect of metformin on GBM progression or survival. Indeed, if this plausible confounding bias were also prevailing within the first three months of survival, then it stands to reason that benefits of metformin during that period might have been masked in our analyses. These findings underscore the need for future research incorporating detailed clinical and metabolic measures to clarify whether metformin has any role in GBM outcomes.

This study has several limitations, largely attributable to its retrospective observational design and reliance on administrative claims data. First, the observational nature of the study precludes any definitive conclusions about causality. Second, the use of SEER-Medicare data introduces the potential for misclassification and is inherently limited by the lack of granular clinical and molecular information that are critical prognostic factors in GBM. For example, variables such as MGMT promoter methylation status, IDH mutation, extent of surgical resection, choice and intensity of adjuvant therapies, or Karnofsky performance status were unavailable in this dataset—all of which may influence both survival outcomes and metformin prescribing patterns. Although SEER-Medicare database provides cause-specific death recodes, these variables are known to be prone to misclassification. In our cohort, nearly all deaths (97%) were classified as cancer-related, suggesting limited reliability for distinguishing neuro-oncologic from non-cancer causes of death. For this reason, we relied on all-cause mortality as the most robust and interpretable outcome available in SEER-Medicare. Third, the study population included only patients aged 66 years and older who were enrolled in SEER-Medicare, which may limit the generalizability of these findings to younger individuals with GBM. Tumor biology and treatment tolerance often differ in younger adults, who may present with distinct molecular profiles and greater capacity to tolerate aggressive therapies, potentially leading to different clinical trajectories and better survival outcomes.[21] Despite extensive covariate adjustment, including for comorbidities and cancer treatments, residual confounding from unmeasured variables—such as glycemic control, duration and severity of diabetes, functional status, or cancer-associated cachexia—cannot be excluded. Forth, although we modeled metformin exposure as a time-varying covariate to minimize immortal time bias, exposure misclassification may still exist. Pharmacy claims data do not capture inpatient medication use or actual medication adherence to prescribed therapies and therefore may not accurately reflect metformin exposure over time. As a result, variations in adherence could have attenuated any true therapeutic association between metformin use and survival outcomes, particularly in patients who discontinued treatment due to disease progression or declining health.

In this context, an emulated target trial could provide a more rigorous framework for causal inference by specifying eligibility criteria, treatment strategies, and a defined time zero—thereby mitigating immortal time bias and strengthening internal validity. However, our dataset lacked critical information, including metabolic biomarkers, cancer progression metrics, functional status, and precise metformin initiation dates. Additionally, such an approach would have required restricting the cohort to patients with no prior exposure to metformin or other antidiabetic medications, which would have markedly reduced the sample size. In our cohort, 13.6% used metformin before diagnosis and 17.7% after, among whom only 23.5% were metformin-naïve at diagnosis. This restriction would have limited statistical power and likely precluded meaningful inference. As real-world datasets evolve to include more granular clinical, metabolic, and treatment timing information, such designs may become increasingly feasible.

To address these complexities, future research should incorporate robust methodological strategies, including prospective data collection on diabetes severity, glycemic control, and cancer-related cachexia. Stratification by baseline metabolic status and precise timing of metformin initiation will be essential. Ultimately, large-scale randomized controlled trials with biologically informed eligibility criteria are needed to isolate metformin's potential therapeutic effects in GBM.

Conclusion

In this large population-based study of older adults with glioblastoma, metformin exposure following diagnosis was not associated with improved survival and was linked to a modestly increased mortality hazard beyond the initial three months. These findings underscore the gap between promising preclinical evidence and clinical outcomes in GBM, highlighting the challenges of translating antitumor effects of metformin into meaningful benefit for patients. Prospective studies with rigorous design and biologically informed selection criteria are needed to clarify the role, if any, of metformin in the management of this aggressive malignancy.

Ethics

The Thomas Jefferson University Institutional Review Board (IRB) reviewed this study and determined that it did not constitute human subjects research (IRB determination letter dated January 12, 2022). Therefore, ethics approval and informed consent were not required in accordance with institutional policies and U.S. federal regulations (45 CFR 46). The study was nevertheless conducted in accordance with institutional guidelines and the principles of the Declaration of Helsinki.

Supplementary Material

Supplementary material is available online at *Neuro-Oncology Advances* (https://academic.oup.com/noa).

Keywords

glioblastoma | metformin | survival | Surveillance, Epidemiology, and End Results (SEER)-Medicare database

Author Contributions

R.S., P.J.M., S.W.K., I.A., R.H., W.S., and V.M. designed the study. W.S. and P.J.M. acquired the data. R.S. and P.J.M. managed the data. R.S., M.L., P.J.M, and S.W.K. performed the statistical analysis. All authors analyzed and interpreted the data. R.S., M.L., S.W.K., and V.M. drafted the manuscript. All authors provided critical revisions of the manuscript for important intellectual content. All authors reviewed the manuscript. The authors read and approved the final manuscript.

Conflict of Interest Statement

The authors declare no conflicts of interest, including financial interests, relationships, or affiliations relevant to the subject matter of this manuscript. This research was conducted as part of the doctoral dissertation of Roshani Shah, MPH, PhD, in the PhD in Population Health Program at Thomas Jefferson University. At the time of this research, Dr. Shah was employed by Pfizer.

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Data Availability

This study used the linked SEER-Medicare database. These data are not publicly available due to restrictions imposed by the Data Use Agreement governing SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the National Cancer Institute; Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database. Certain limitations exist regarding the use of these data, and we have taken steps to ensure data confidentiality and protect patient privacy. Specifically, we have not attempted to identify individuals or their providers and have suppressed any findings that might allow for such identification according to the SEER-Medicare database requirements.

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