

Assessment of the Correlation Between Hypoalbuminemia and Adverse Effects of Oral Anticancer Medications in Adult Patients with Solid Tumors: A Single-Center Retrospective Cohort Study in Saudi Arabia

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Background: Hypoalbuminemia is commonly seen in cancer patients. Albumin is essential in drug binding and distribution, particularly in medications with a binding affinity of $\geq 95\%$ such as tyrosine kinase inhibitors (TKIs). However, hypoalbuminemia can cause an increase in free drug concentration of highly protein-bound drugs, which can enhance drug exposure and cause adverse events. Hypoalbuminemia can significantly affect pharmacokinetics, increasing free drug concentrations and unbound drug in plasma as a consequence of low albumin levels. These alterations in pharmacokinetics can affect patients' tolerability to medications. The study aims to elucidate the impact of albumin levels on medication tolerability and the incidence of adverse events in adult patients with solid tumors.

Methods: A retrospective cohort study was conducted of all adult patients with solid tumors receiving tyrosine kinase inhibitors (TKIs) with $\geq 95\%$ protein binding at the Ministry of National Guards Health Affairs-affiliated hospitals, Riyadh, Saudi Arabia. Electronic medical records were reviewed to identify eligible patients initiated on TKIs between January 1, 2016 and December 31, 2022. The main outcomes of this study were survival proportions, grading adverse events, and treatment failure rates in relation to albumin levels.

Results: The study included 127 patients out of 450 patients receiving 19 oral TKIs and were divided into two groups (Group A: 51.2% with hypoalbuminemia, and Group B: 48.8% without hypoalbuminemia). Results reveal a significant correlation between hypoalbuminemia and decreased survival proportions by 22% (p -value = 0.04). Additionally, the study identifies a pattern in severity of adverse events, with grade 1 being the most common. Treatment failure is observed more frequently in patients with hypoalbuminemia compared to those with normal albumin levels.

Conclusion: This study conducted among a Saudi population demonstrates the critical role of serum albumin levels in predicting TKIs tolerability and treatment success in patients with solid tumors. Assessing and addressing nutritional status and serum albumin before and during TKI treatment may help clinicians identify high-risk patients and optimize supportive care. Larger prospective studies in diverse populations are needed to validate these findings.

Keywords: hypoalbuminemia, liver disease, solid tumors, protein-bound drug, serum albumin, TKI discontinuation, TKI tolerability, tyrosine kinase inhibitor

Introduction

Albumin is the most abundant protein in the human body. Albumin plays a crucial role in regulating the pharmacokinetics and pharmacodynamics of drugs by binding to them, facilitating transport, and serving as a depot.^{1,2} Hypoalbuminemia is commonly seen in cancer patients due to tumor necrosis and tissue destruction.³ According to the Common Terminology Criteria for Adverse Events (CTCAE), grades are assigned based on albumin levels and severity: grade 1 (mild), 3.0 g/dL to the lower limit of normal; grade 2 (moderate), 2 to 3 g/dL; grade 3 (severe), less than 2 g/dL; grade 4, life-threatening; and grade 5, death.⁴ In patients with hypoalbuminemia, higher levels of the unbound (free) drug may become available to bind to the receptor, thereby potentially amplifying the pharmacological response.⁵ However, a significant elevation in free-drug concentration might cause toxicities, require dosage adjustments or medication discontinuation, and exacerbate the severity of drug interactions.^{5,6} Most of the currently orally administered targeted oncolytic medications, such as tyrosine kinase inhibitors (TKIs), eg, sorafenib, osimertinib, erlotinib, and lapatinib, and anti-androgens, have severe adverse effect profiles and are highly protein bound. Therefore, these highly protein-bound medications may produce a higher pharmacological and toxic response in solid tumor cancer patients if albumin levels are reduced.⁶ Oral oncolytic may be replaced by highly protein-bound non-oncolytic drugs (or vice versa) when administered concurrently. This drug–drug interaction may result in a greater concentration of free drug and might have an impact on toxicity and result in amplified effects in individuals with hypoalbuminemia. When initiating a new treatment regimen, it is still advisable to assess any potential protein displacements even if the therapeutic relevance of protein-binding displacement has been questioned.⁷

Several larger studies have further characterized the association between hypoalbuminemia and TKI tolerability.^{8–12} A study conducted in adult patients with solid tumor malignancies found that adverse events following oncolytic therapy in both patients with hypoalbuminemia and with normal albumin levels were common. However, in patients with hypoalbuminemia, the time to medication discontinuation due to verified toxicity was significantly shorter, suggesting that hypoalbuminemia is a significant risk factor for a shorter time to discontinuation due to documented adverse effects.⁸ Another retrospective study found that those with solid tumor malignancies and hypoalbuminemia had a lower performance status as well as a larger percentage of baseline liver disease and proteinuria compared to patients with normal albumin level.⁹ This resulted in intolerability of oncolytic drugs adverse effects, significantly higher treatment discontinuation, and shorter treatment time. Altogether, indicating that when starting TKIs, baseline hypoalbuminemia may be a crucial clinical evaluation. Another retrospective study of 220 solid tumor patients receiving oral TKIs found that baseline hypoalbuminemia was associated with worse performance status and more liver disease and proteinuria; treatment discontinuation occurred in 83% of hypoalbuminemic patients versus 60% of patients with normal albumin, and time to discontinuation was markedly shorter of 96 days vs 288 days.¹¹ More recently, a 2024 report involving 282 patients demonstrated that those with hypoalbuminemia experienced a shorter median treatment duration (2.8 vs 4.3 months) and a higher incidence of grade 3/4 adverse events (73% vs 27%) compared with patients who had normal albumin levels.¹² All of these studies show the potential for hypoalbuminemia to influence TKI tolerability and treatment continuity.

Despite these global data, to our knowledge, evidence from Middle Eastern countries is lacking on the possible effects of hypoalbuminemia on highly protein-bound oral oncolytic drugs in adult patients with solid tumors in Saudi Arabia. This study aims to assess the effect of hypoalbuminemia on drug tolerability in adult patients treated with highly protein-bound targeted oral oncolytic therapy at one of the Ministry of National Guard Health Affairs (MNGHA) affiliated hospitals.

Materials and Methods

Study Design and Setting

This retrospective, single-center cohort study included adult patients with solid tumors treated with highly protein-bound ($\geq 95\%$ protein binding) Tyrosine Kinase Inhibitors (TKIs) at a Ministry of National Guard Health Affairs-affiliated tertiary hospital. The study period was between January 1, 2016, to December 31, 2022. This study was approved by the King Abdullah Medical Research Center (KAIMRC) Institutional Review Board (SP23R/144/06). The study was

conducted in accordance with ethical principles derived from the Declaration of Helsinki. Given the retrospective nature of data review, informed consent was waived, and all patient information was handled in compliance with institutional privacy regulations.

Eligibility Criteria

A total of 450 adult patients newly initiated on TKIs were screened for study eligibility through electronic record review using BESTCare 2.0. The final analytic cohort consisted of 127 patients who met all inclusion criteria (Figure 1).

Data Collection and Variables

Baseline demographic and clinical data were extracted from BESTCare 2.0 and documented using secure data collection forms managed on Google Forms. Variables collected at TKI initiation included age, sex, weight, height, performance status, cancer type and stage, prior therapy lines, proteinuria status, baseline albumin, prescribed oral TKI regimen (dose and frequency), and history of liver or kidney disease. Patients were stratified into two groups based on baseline serum albumin, with hypoalbuminemia defined as <3.5 g/dL per institutional criteria.

TKI Medications Included

The analysis included adult patients receiving highly protein-bound oral tyrosine kinase inhibitors, identified through confirmed prescriptions in the institutional EHR. The TKIs assessed were Axitinib, Pazopanib, Sorafenib, Alectinib, Cabozantinib, Erdafitinib, Lapatinib, Neratinib, Regorafenib, Dasatinib, Lenvatinib, Erlotinib, Sunitinib, and Osimertinib. Agents were selected based on documented high protein-binding profiles consistent with the study's inclusion focus.

Clinical Function Screening

Hepatic dysfunction was defined as ALT or AST $>2.5 \times$ ULN, or total bilirubin $>1.5 \times$ ULN, with bilirubin $>3 \times$ ULN considered in patients with documented Gilbert syndrome. Renal dysfunction was confirmed by prior diagnosis of kidney impairment (eg, chronic kidney disease) or serum creatinine $>1.5 \times$ ULN, followed by creatinine clearance estimation using the Cockcroft–Gault equation when applicable, where a value <50 mL/min supported renal dysfunction classification.

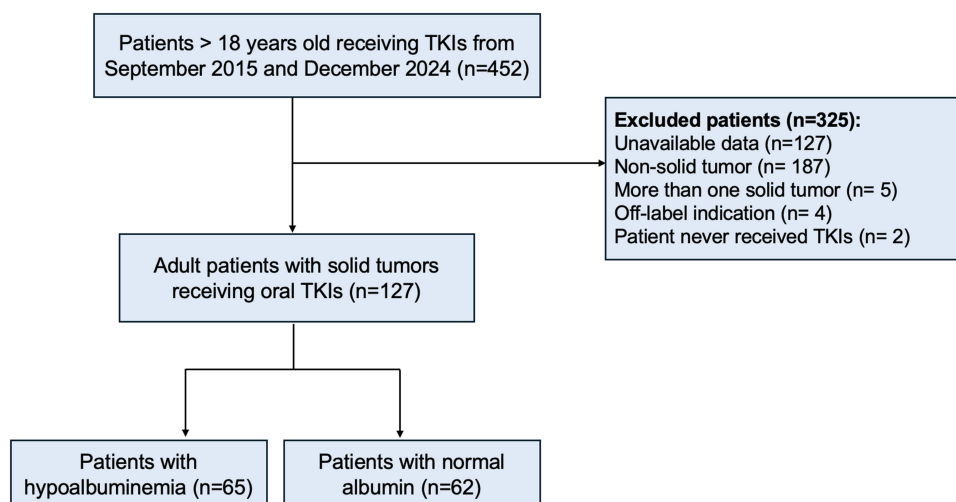


Figure 1 Flowchart of Inclusion and Exclusion Criteria.

Outcomes and Severity Classification

Primary outcomes included overall survival proportions, adverse event severity, and TKI treatment failure in relation to baseline albumin. Treatment failure was defined as permanent TKI discontinuation or therapeutic change due to disease progression, lack of clinical benefit, intolerability, illness, or non-probability-related dose-limiting toxicity. Adverse events were graded using CTCAE v5.0, where Grades 1–2 reflected mild to moderate clinical severity and Grades 3–5 represented severe or irreversible outcomes. Additional analytic data included incidence and timing of any-grade adverse events, TKI dose reductions or interruptions (dates, causes, and duration), albumin at each adverse event, discontinuation dates, and failure outcomes resulting in death.

Treatment and Clinical Verification

Treatment initiation and discontinuation dates were verified using progress notes documented by consultants in the electronic health record and cross-referenced against the medication lists in BESTCare 2.0. Adverse effects were extracted from routinely documented progress notes entered by either residents or consultants, based on clinical encounter records in the same system. For consistency and data integrity, adverse event grading and timelines were double-checked against recorded medication changes and clinical narratives at the time of each event, ensuring chronological alignment. Adherence to therapy could not be quantitatively or systematically assessed due to the absence of standardized adherence documentation in patient files and was therefore acknowledged as a study limitation. Side effects were considered as recorded when documented in progress notes by residents or consultants during routine patient care.

Statistical Analysis

Continuous variables were presented as means with standard deviations (SD) and median with interquartile range (IQR), while nominal variables were expressed as counts with percentages. Comparisons between the groups (Hypoalbuminemia vs. Normal albumin) were performed either a *t*-test or a Mann–Whitney *U*-test and categorical variables were compared using chi-square or Fisher's exact tests. The multivariable analysis was performed based on the variables that were significant at the univariate and the results were presented as odds ratios with 95% confidence levels. Cox regression analysis was employed to assess the relationship between hypoalbuminemia and the primary outcome (ie, all-cause TKI discontinuation), adjusting for covariates such as performance status, prior lines of therapy, baseline metastases, and liver disease. The covariates were selected based on prior research indicating their potential impact on hypoalbuminemia and disease severity, potentially confounding the outcome of treatment discontinuation.^{8,10,11} Significance was defined as $p < 0.05$. Statistical analyses were conducted using SPSS version 25.0.

Results

Out of 452 patients, 127 were included in the study and categorized into two groups based on serum albumin levels: 65 with hypoalbuminemia and 62 with normal albumin (Figure 1). In terms on baseline characteristics, gender distribution showed that 50.97% were female (Table 1). The distribution of solid tumor types is as follows: 29.9% non-small cell lung cancer, 26.7% hepatocellular carcinoma, 11.8% renal cell carcinoma, 10.23% breast cancer, 7.8% thyroid cancer, and 7.8% other cancers. Additionally, 70.08% of solid tumor cancer patients had stage 4 cancer, 3.15% had stage 3, and 26.77% had an unknown cancer stage. In terms of Eastern Cooperative Oncology Group (ECOG) performance status, while 30% scored 0 and 1, 33% scored 2 and more, 37% Unknown score. Majority of patients had advanced disease with metastases in both groups (95.8% vs 95.6%). Sorafenib was the most frequently used TKI at 26.77%, followed by osimertinib at 13.3% (Table 2). The majority of patients (83.9%) received TKI medications once daily, while 16.1% were administered twice daily. Regarding treatment lines, 54% received TKIs as first-line medication, 27.4% as second line, 11.3% as third line, and 7.3% as fourth line or beyond. Prior to TKI initiation, 51.2% of patients presented with baseline hypoalbuminemia, whereas 48.8% exhibited normal baseline albumin levels. More than half (65.3%) of patients experienced adverse events from TKIs, with 34.7% reported no adverse events.

Table 1 Baseline Characteristics of the Included Patients (n = 127)

Variable	Hypoalbuminemia (n=65, 51.2%)	Normal Albumin [†] (n=62, 48.8%)	p-value
Gender, n (%)			
Male	38 (58.5%)	25 (40.3%)	0.041
Female	27 (41.5%)	37 (59.7%)	
Age (in years)			
Mean ± (SD)	62.5 ± (12.9)	60.0 ± (16.6)	0.352
Median (range, IQR)	63.0 (21–85, 17)	60.0 (19–92, 21.5)	
Age (in years)			
<65	35 (53.8%)	37 (59.7%)	0.507
≥65	30 (46.2%)	25 (40.3%)	
BMI (in kg/m ²)			
Mean ± (SD)	24.3 ± (5.0)	26.1 ± (6.6)	0.098
Median (range, IQR)	24.0 (15–37, 7.1)	25.3 (15–43, 8.7)	
Cancer type, n (%)			
Breast Cancer	4 (6.2%)	9 (14.5%)	0.351
Colorectal Cancer	4 (6.2%)	3 (4.8%)	
Hepatocellular carcinoma	19 (29.2%)	15 (24.2%)	
Non-small-cell lung cancer	20 (30.8%)	18 (29.0%)	
Renal Cell Carcinoma	10 (15.4%)	5 (8.1%)	
Thyroid Cancer	5 (7.7%)	5 (8.1%)	
Others	3 (4.6%)	7 (11.3%)	
Cancer Stage, n (%)			
Stage I/II [‡]	0 (0.0%)	0 (0.0%)	0.947
Stage III	2 (4.2%)	2 (4.4%)	
Stage IV	46 (95.8%)	43 (95.6%)	
Not identified (n=34) [‡]	(n=17)	(n=17)	
ECOG Performance Status, n (%)			
0 or I	14 (35.0%)	24 (60.0%)	0.025
≥2	26 (65.0%)	16 (40.0%)	
Missing data (n=47) [‡]	(n=25)	(n=22)	
Baseline Albumin level (in g/L)			
Mean ± (SD)	29.2 ± (3.3)	39.0 ± (2.8)	<0.001
Median (range, IQR)	30.0 (16–34, 3.0)	39.0 (35–47, 4.8)	
Grade of baseline albumin (prior to starting TKI), n (%)			
Normal (≥ 35 to 50 g/L)	0 (0.0%)	62 (100.0%)	<0.001
Mild (30 to < 35 g/L)	34 (52.3%)	0 (0.0%)	
Moderate (20 to < 30 g/L)	30 (46.2%)	0 (0.0%)	
Severe (< 20 g/L)	1 (1.5%)	0 (0.0%)	
History of Co-morbidities, n (%)			
Proteinuria	1 (1.5%)	1 (1.6%)	0.973
Liver dysfunction or cirrhosis	23 (35.4%)	15 (24.2%)	0.169
Renal dysfunction	12 (18.5%)	5 (8.1%)	0.025

Notes: [†]The normal albumin range for adults before initiating TKI therapy was considered at 35–50 g/L. [‡]Variables with either a value of zero or missing data were excluded from statistical calculations.

Table 2 Distribution of TKI Therapy Among Patients

TKI Therapy Used n (%)	Hypoalbuminemia (n=65)	Normal Albumin (n=62)	P-value
Sorafenib	18 (27.7%)	16 (25.8%)	0.683
Osimertinib	9 (13.8%)	8 (12.9%)	
Lapatinib	5 (7.7%)	9 (14.5%)	
Others^a	33 (50.8%)	29 (46.8%)	

Notes: ^aOther TKIs included axitinib, pazopanib, alectinib, cabozantinib, erdafitinib, neratinib, regorafenib, dasatinib, gefitinib, lenvatinib, afatinib, crizotinib, erlotinib, imatinib, and nilotinib.

Table 3 Adverse Events in Patients Treated with TKI Therapy

Adverse Events [†] , n (%)	Overall (n=127)	Hypoalbuminemia (n=65)	Normal Albumin (n=62)	p-value
None [†]	44 (34.6%)	23 (35.4%)	21 (33.9%)	0.858
Any grade	83 (65.4%)	42 (64.6%)	41 (66.1%)	
Grade > 2 [¶]	10 (7.9%)	4 (6.2%)	6 (9.7%)	0.487
Diarrhea	17 (13.4%)	7 (10.8%)	10 (16.1%)	0.440
Nausea	14 (11.0%)	8 (12.3%)	6 (9.7%)	0.779
Vomiting	19 (15.0%)	9 (13.8%)	10 (16.1%)	0.806
Anemia	30 (23.6%)	24 (36.9%)	6 (9.7%)	<0.001
Thrombocytopenia	14 (11.0%)	9 (13.8%)	5 (8.1%)	0.398
Neutropenia	4 (3.1%)	4 (6.2%)	0 (0.0%)	0.120
CV (HTN, arrhythmia)	9 (7.1%)	2 (3.1%)	7 (11.3%)	0.091
Myalgia/arthralgia	9 (7.1%)	3 (4.6%)	6 (9.7%)	0.317
TKI therapy withheld	33 (26.0%)	19(29.2%)	14(22.6%)	0.393

Notes: [†]Percentages are calculated from the total number of patients in the corresponding group. [¶] Missing data were excluded from statistical calculations.

Adverse event grading using the CTCAE criteria demonstrated that 42% had unknown grading, 29.8% were classified as grade 1, 15.5% as grade 2, 10.7% as grade 3, and 1.2% as grade 4 (Table 3), (Figure 2). In terms of treatment outcomes, 60.63% of patients experienced treatment failure, while 39.37% did not. Lastly, 57.48% of the patients died and 42.52% survived.

Looking at Kaplan–Meier survival analysis, which stratified by serum albumin levels prior to initiating TKI therapy, a significant difference in overall survival between patients with hypoalbuminemia and those with normal albumin levels (Figure 3). The median overall survival (OS) in the hypoalbuminemia group was 0.605 years, whereas the median OS in the normal albumin group was not reached, as the survival curve did not drop below 50% during the follow-up period. The Log rank test demonstrated a statistically significant difference in survival between the two groups, with a hazard ratio of 2.216 (95% CI: 1.36–3.60; $p = 0.001$), indicating that patients with hypoalbuminemia had more than double the risk of mortality compared to those with normal albumin levels. To assess the effect of TKI therapy on albumin levels, a paired t -test was conducted comparing pre- and post-treatment albumin concentrations within each group (Figure 4). In patients with normal baseline albumin levels, there was a statistically significant reduction in albumin following TKI treatment ($p < 0.001$). In contrast, no significant change was observed in the hypoalbuminemia group ($p = 0.780$),

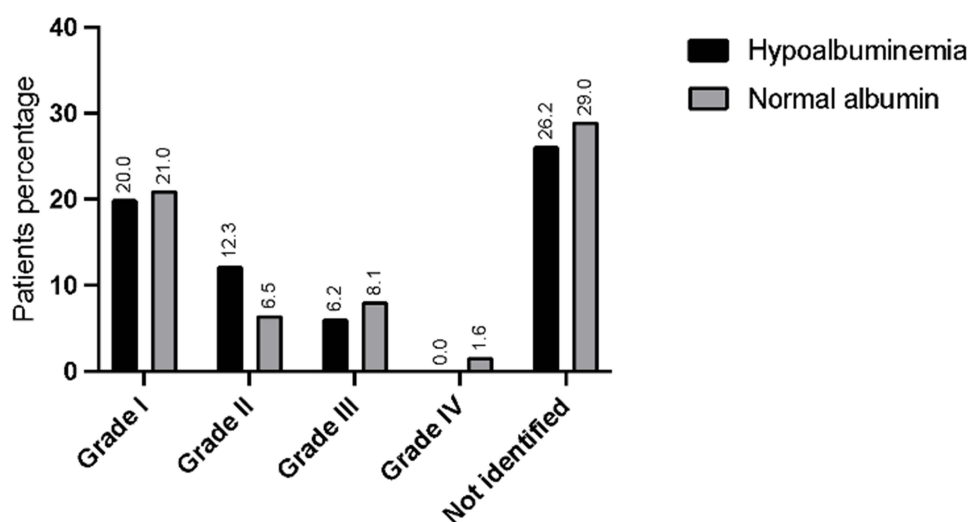


Figure 2 Adverse events grading per CTCAE in hypoalbuminemia group vs normal albumin group. The Fisher's exact test showed no statistically significant differences between groups ($p=0.725$).

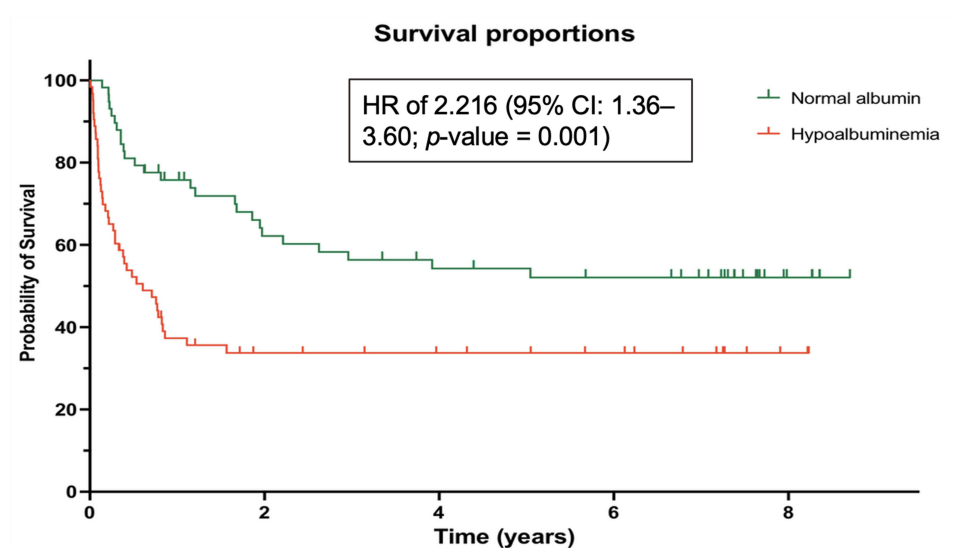


Figure 3 Kaplan-Meier survival analysis stratified by hypoalbuminemia status prior to starting TKI therapy.

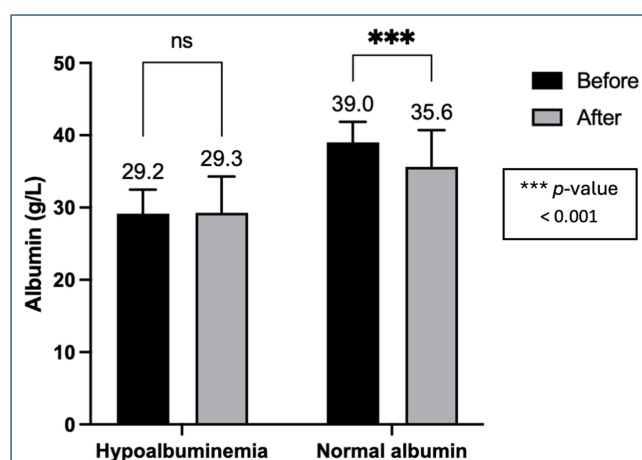


Figure 4 Pre- and post-TKI therapy albumin levels in solid cancer patients.

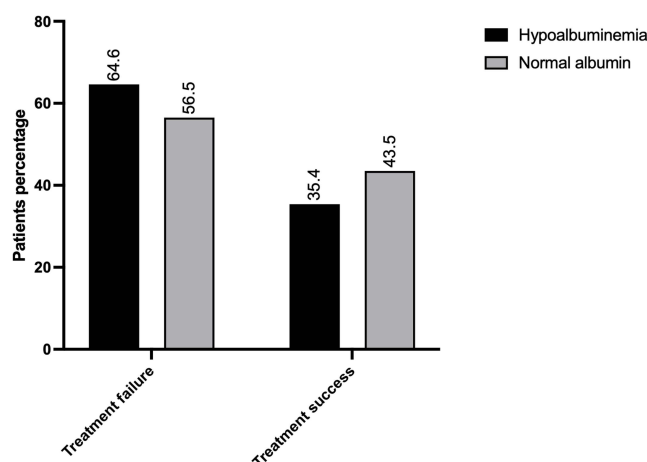


Figure 5 Treatment failure and success of TKIs in hypoalbuminemia group vs normal albumin group ($p=0.369$).

suggesting that TKI treatment may have a greater impact on albumin levels among patients with initially normal nutritional status. Additionally, we examined treatment response by albumin status, comparing rates of TKI treatment success and failure between the two groups (Figure 5). Although the hypoalbuminemia group showed a higher proportion of treatment failure (43/65 vs.34/62), the difference was not statistically significant ($p = 0.192$). This suggests that while hypoalbuminemia is associated with worse overall survival, it may not directly predict treatment response to TKIs. The adjusted multivariable logistic regression is presented in Table 4. The anemic patients had significantly 3.65 (95% CI: 1.04–12.81) times higher odds of having hypoalbuminemia compared with non-anemic patients ($p=0.04$).

Discussion

This study aimed to assess the association of hypoalbuminemia and adverse effects with oral anticancer medications. Our results showed that baseline hypoalbuminemia was associated with markedly worse overall survival and a higher rate of treatment failure and discontinuation. Although the overall incidence of adverse events did not differ between groups, anemia was more frequent in the hypoalbuminemia group. These findings suggest that low serum albumin at baseline might be an important predictor of poor outcomes in patients receiving highly protein-bound TKIs. A few studies have shown that some TKIs are highly protein-bound and could lead to toxicities in patients with hypoalbuminemia.^{8,11,12} One explanation is that a larger percentage of the medication is pharmacologically active and unbound in hypoalbuminemia which increase the likelihood of toxicities. In regard to advanced cancers, we found that most patients had a higher incidence of metastases at baseline in both groups.

One study established that hypoalbuminemia is closely associated with nutritional risk and the presence of systemic inflammation.¹³ This study highlights the fact that hypoalbuminemia is not just an indicator of less than desirable nutritional status but it is also an indicator of chronic inflammation within the body, stressing its dual role as an indicator of nutrition and inflammation status. To investigate further the clinical importance of hypoalbuminemia, particularly for

Table 4 Multivariable Analysis

Variables	OR (95% CI)	p-value
Gender (Male)	2.48 (0.82–7.51)	0.11
ECOG Performance Status (≥ 2)	2.73 (0.92–8.12)	0.07
Anemia	3.65 (1.04–12.81)	0.04
Renal dysfunction	1.93 (0.32–11.55)	0.47

anticancer targeted therapies, two further studies assessed the impact of low albumin levels on TKI tolerability and efficacy.^{11,12} As yet, there is minimal robust evidence that specifically addresses hypoalbuminemia as a predictor of TKI tolerability, and hence it remains an important restriction on our understanding of the impact of hypoalbuminemia on oncology patient treatment outcomes from these medications.

While the majority of patients in our study experienced an adverse event of any grade, the incidence of adverse events was comparable in the two groups. There is currently minimal information available about the relationship between hypoalbuminemia and cancer patients' ability to tolerate TKIs. Murdock et al performed a retrospective study to evaluate highly protein-bound oral oncolytic medication tolerability in solid tumors.⁸ According to their analysis, the groups had comparable incidences of adverse events (81% with hypoalbuminemia vs. 75% without hypoalbuminemia), and the group with hypoalbuminemia had a significantly shorter time to TKI discontinuation (4.2 months vs. 13.1 months, respectively) and a higher incidence of all-cause TKI discontinuation (83% vs. 57%, respectively).

This retrospective cohort study was subject to few limitations. The data collection for the assessment of adverse events and the cause of TKI discontinuation was dependent on provider documentation due to the retrospective design of the study with a possibility that not all adverse events were documented. Moreover, the effect on specific dates for the occurrence of adverse events is an additional limitation of this study's retrospective design. Additionally, adherence could not be quantified due to the nature of the study design. Also, the small sample size in addition to the heterogeneity of our group with multiple cancer types is other limitation of this study. We also excluded patients without a recorded baseline albumin, which may introduce selection bias. This study represents an initial step towards a broader investigation in Saudi Arabia; thus, future research efforts should consider the identified limitations identified in this study. Additionally, future studies should explore whether albumin guided strategies such as nutritional support or closer monitoring can improve treatment outcomes. Investigating the pharmacokinetic effects of hypoalbuminemia on free-drug levels may also help guide dosing or supportive interventions.

Conclusion

This study is the first to evaluate the impact of hypoalbuminemia on the tolerability of highly protein-bound TKIs in a Saudi population. We found that low albumin levels were associated with poorer survival and a higher likelihood of treatment failure. These findings demonstrate the value of baseline and ongoing albumin assessment in patients starting TKIs. Future multi-center prospective studies are warranted to validate our findings and refine albumin-guided interventions. Future utilization of albumin level as a monitoring tool to identify individuals who may benefit from nutritional support or dose adjustments rather than withholding therapy. Integrating albumin monitoring into routine care could help personalize TKI dosing and improve outcomes.

Disclosure

The authors report no conflicts of interest in this work.

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