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ORIGINAL ARTICLE

Risk factors for persistent wound drainage after hemiarthroplasty in elderly hip fracture patients

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ABSTRACT

Objectives: This study aims to evaluate the risk factors for persistent wound drainage (PWD) and its impact on in-hospital outcomes among geriatric patients with hip fractures treated with hemiarthroplasty.

Patients and methods: A total of 265 hip fracture patients (91 males, 174 females; median age: 83 years; range, 65 to 99 years) who underwent hip hemiarthroplasty between June 2019 and June 2025 were retrospectively analyzed. Demographics, comorbidities, laboratory findings, and preoperative medications were evaluated. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of PWD.

Results: Sixty-one (23.0%) patients were diagnosed with PWD. Low postoperative Day 1 serum albumin level (odds ratio [OR] = 0.85, 95% confidence interval [CI]: 0.79-0.92, $p < 0.001$), preexisting hypertension (OR = 2.50, 95% CI 1.15-5.39, $p = 0.020$), and chronic warfarin use (OR = 8.15, 95% CI 2.20-30.14, $p = 0.002$) were identified as independent predictors of PWD. The optimal cut-off for the postoperative Day 1 serum albumin level was 30.5 g/L (sensitivity: 60.7%, specificity: 76.5%). In the PWD group, in-hospital mortality rates (16.4% *vs.* 5.9%, $p = 0.009$), mean length of hospital stay (17.7 ± 11.8 days *vs.* 7.4 ± 6.3 days, $p = 0.000$), and the incidence of sacral decubitus ulcers (26.2% *vs.* 10.8%, $p = 0.003$) were significantly higher. Rates of both superficial and deep wound infections were also significantly elevated in the PWD group ($p < 0.001$ and $p = 0.003$, respectively).

Conclusion: Low postoperative albumin, preexisting hypertension, and chronic warfarin use are significant predictors of PWD following hemiarthroplasty in elderly patients with hip fractures, and the existence of PWD was associated with increased in-hospital morbidity and mortality. Early identification and preventive strategies targeting at-risk patients may improve outcomes.

Keywords: Hemiarthroplasty, hip fracture, periprosthetic joint infection; persistent wound drainage, risk factors.

Hip fractures are common and devastating injuries in the geriatric population, associated with high rates of morbidity and mortality.[1] As the global population continues to age, the incidence of hip fractures is projected to increase, placing a growing burden on healthcare systems worldwide.[2] In most cases, hemiarthroplasty is the preferred surgical treatment aiming to restore mobility and maintain functional independence as soon as possible. Unfortunately, postoperative complications can sometimes hinder recovery and negatively impact long-term outcomes. Among these complications, persistent wound drainage (PWD) is of particular concern due to its association with delayed wound healing and an increased risk of infection.

Although PWD may occur after various orthopedic procedures, it is particularly concerning in the context of joint arthroplasty due to its strong association with serious complications such as periprosthetic joint infection (PJI).[3-5] It is a severe and potentially devastating postoperative complication that can necessitate revision

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surgery, prolong hospitalization, increase healthcare costs, and result in substantial patient morbidity.[6,7] Despite its clinical significance, there is no universally accepted definition of PWD; it is usually described as wound drainage that persists beyond a specific postoperative time frame.[4] This lack of standardization contributes to the absence of evidence-based guidelines for its diagnosis and management.[3]

Numerous studies have explored the risk factors and management strategies associated with PWD. Shahi et al.[5] identified hypothyroidism, diabetes, rheumatoid arthritis, morbid obesity, female sex, and chronic alcohol use as significant predictors of PWD following total hip and knee arthroplasty. Similarly, Yang et al.[8] reported that low serum albumin levels, elevated body mass index (BMI), and higher American Society of Anesthesiologists (ASA) classes were associated with increased risk of surgical site infection.[8] However, most of this research has focused on patients undergoing elective total joint arthroplasty in the general population, with limited evidence addressing predictors of PWD specifically in geriatric patients with hip fractures. This population presents unique clinical challenges due to age-related physiological changes, multiple comorbidities, and compromised nutritional, status all of which may increase vulnerability to complications such as PWD.[9]

In the present study, we aimed to identify predictors of PWD in geriatric hip fracture patients treated with hemiarthroplasty and to evaluate its impact on in-hospital outcomes, including mortality, complications, and length of stay.

PATIENTS AND METHODS

This single-center, retrospective cohort study was conducted at Ankara Bilkent City Hospital, Department of Orthopedics and Traumatology between June 2019 and June 2025. Of a total of 271 consecutive patients, 265 (91 males, 174 females; median age: 83 years; range, 65 to 99 years) who underwent hip hemiarthroplasty for acute hip fractures were included. Exclusion criteria were death within the first three postoperative days, missing data, and fractures older than 21 days. Six patients were excluded; two had fractures older than 21 days, two died within the first three postoperative days, and two had incomplete data. Written informed consent was obtained from each patient. The study protocol was approved by the Ankara Bilkent City Hospital Ethics Committee (Date: 07.05.2025, No: TABED 1-25-1266). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Potential perioperative predictors of PWD were identified based on previously published literature.[10,11] Data collected included age, sex, BMI, preoperative laboratory values (lymphocyte count, hemoglobin, platelet count, and neutrophil-to-lymphocyte ratio), comorbidities, smoking status, steroid use, chronic alcohol consumption, anticoagulant use, ASA class, surgical delay, operative time, and fracture type (AO/OTA 31A or B). Serum albumin levels were recorded at admission and on postoperative Day 1. Preexisting hypertension was defined as having a documented history of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg in the medical records, or the use of antihypertensive medication prior to hospital admission.[12] Comorbidities were quantified using the Charlson Comorbidity Index (CCI), categorized as 0 (none), 1 (low), or ≥ 2 (high) according to previous studies.[13,14]

Perioperative anticoagulation and antiplatelet management followed current clinical guidelines.[15] Consistent with these recommendations, direct oral anticoagulants were typically withheld for a minimum of 36 h prior to surgery, while antiplatelet agents and warfarin were managed to ensure appropriate coagulation parameters without delaying surgical intervention. All other medication adjustments were meticulously coordinated with anesthesiology and relevant specialties to optimize patient safety and patient outcomes.

All operations were performed using the Watson-Jones approach by the same surgical team. Two types of uncemented femoral stems were used based on fracture morphology and patient bone quality: a square cross-sectional stem and the Wagner SL revision stem (Zimmer Biomet, Warsaw, IN, USA).

The type of anesthesia was determined by the anesthesiology team; however, spinal anesthesia was predominantly used, in accordance with current recommendations for geriatric patients with hip fractures.[16] Prophylactic cefazolin (1 g) was administered preoperatively and every 8 h for 24 h postoperatively. For the prevention of venous thromboembolism, low-molecular-weight heparin (LMWH) was initiated 12 to 24 h postoperatively after hemostasis was established, typically at a dose of 40 mg subcutaneously once daily, and continued

for 10 to 14 days, or up to 35 days in high-risk patients. Hemovac® drains were routinely placed in all patients and were removed within 24 to 48 h postoperatively.

The primary outcome was the incidence of PWD, defined as wound drainage exceeding 2 × 2 cm on the dressing that persisted beyond 72 h postoperatively (Figure 1).[3,17] Secondary outcomes included length of hospital stay, in-hospital complications, and mortality. Dressings were changed daily, and the presence of PWD was assessed daily by the senior chief of the orthopedic department. Patients with drainage lasting more than five days underwent reoperation and continued daily monitoring until resolution.

Statistical analysis

Statistical analysis was performed using the PASW Statistics version 18.0 software (SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented in mean ± standard deviation (SD) or median and interquartile range (IQR), depending on their distribution, while categorical variables were presented in number and frequency. Group comparisons were performed using the Student t-test or the Mann-Whitney U test for continuous variables and the chi-square or Fisher exact test for categorical variables. Variables with a p value of ≤ 0.10[18] in the univariate analysis were subsequently entered into a multivariate logistic regression model to identify independent predictors of PWD. A stepwise backward elimination method was used to refine the model. Bonferroni correction was applied to adjust for multiple comparisons. A p value of < 0.05 was considered statistically significant. To evaluate model performance and identify optimal threshold values for continuous predictors, receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was calculated to assess discriminative power. A post-hoc power analysis was conducted using the ClinCalc software version 1.0. With the probability of a type 1 error (α) = 0.05, the statistical power was calculated as 94.7% for postoperative Day 1 serum albumin, 52.7% for preexisting hypertension, and 93.9% for chronic warfarin use.[19]



FIGURE 1. A case of an 82-year-old woman who developed persistent wound drainage after hip hemiarthroplasty.

RESULTS

Age data for the PWD and non-PWD groups were reported as median (IQR) in Table I as the data did not show a normal distribution. Based on the CCI, 7.5% of patients had a score of 0, 20.4% had a score of 1, and 72.1% had a score of ≥ 2. A total of 61 (23.0%) patients developed PWD, while 204 (77.0%) patients did not.

There were no significant differences between the PWD and non-PWD groups in terms of admission lymphocyte count, platelet count, or neutrophil-to-lymphocyte ratio (p = 0.209, 0.479, and 0.493, respectively). Similarly, age, sex, BMI, ASA class, CCI score, surgical delay, operative time, and preoperative albumin levels were comparable between groups ($p > 0.05$ for all). However, AO-OTA type 31A fractures were more common in the PWD group than in the non-PWD group (73.8% *vs.* 59.8%, p = 0.047). Patients in the PWD group also had significantly lower admission hemoglobin and postoperative Day 1 albumin levels (p = 0.033 and < 0.001, respectively; Table 1).

Preexisting hypertension was present in 82.0% of the PWD group compared to 68.6% in the non-PWD group, indicating a statistically significant difference (p = 0.042). Other comorbidities, including diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, congestive heart failure, rheumatoid arthritis, hypothyroidism, history of cerebrovascular event, dementia, vascular insufficiency, arrhythmia, and malignancy history, showed no statistically significant differences between the groups ($p > 0.05$; Table I).

The use of warfarin was significantly more common in the PWD group (13.1%) compared to the non-PWD group (2.0%) (p < 0.001). No significant differences were observed for the use of other anticoagulants or antiplatelet agents,

TABLE I

Baseline features of the patients with and without persistent wound drainage after hip hemiarthroplasty, univariate analysis

	PWD (n = 61)					Non-PWD (n = 204)					
Variables	n	%	Mean ± SD	Median	IQR	n	%	Mean ± SD	Median	IQR	*p*
Characteristics											
Age (year)				85	80-89				82	78-88	0.073*,a
Sex											0.771[b]
Male	20					71					
Female	41					133					
Side											0.066*,b
Left	36					93					
Right	25					111					
Body mass index (kg/m^2)				26.6	24.2-29.3				25.9	23.2-29.1	0.698[a]
CCI category											0.803[b]
0	4					16					
1	11					43					
≥ 2	46					145					
ASA class											0.328[b]
II	12					29					
III	35					138					
IV	14					37					
Operation duration (min)				55	52-60				55	50-60	0.105[a]
Fracture type (AO-OTA 31A/B)	16/45					82/122					0.047*,b
Delay to surgery (day)				5	3-6				4	2-6	0.270[a]
Laboratory tests											
Preoperative Hb (g/dL)			11.6 ± 1.9					12.2 ± 1.7			0.033*,c
Preoperative lymphocyte count				1.1	0.8-1.7				1.2	0.8-1.8	0.209[a]
Preoperative platelet count				241.0	180.5-287.5				243.0	194.0-293.0	0.479[a]
Preoperative NLR				6.2	3.5-12.3				6.2	3.4-10.3	0.493[a]
Preoperative albumin (g/L)				39.0	34.5-42.0				40.0	37.0-42.0	0.073*,a
Postoperative day one albumin (g/L)				30.0	27.5-34.0				33.0	31.0-35.5	< 0.001*,a
Comorbidities											
Diabetes mellitus	18	29.5				61	29.9				0.953[b]
Chronic obstructive lung disease	12	19.7				30	14.7				0.351[b]
Congestive heart failure	17	27.9				30	14.7				0.018*,b
Chronic renal disease	9	14.8				23	11.3				0.464[b]
Hypothyroidism	11	18.0				27	13.2				0.348[b]
Rheumatoid arthritis	2	3.3				6	2.9				0.892[b]
Cerebrovascular event history	7	11.5				32	15.7				0.415[b]
History of dementia	12	19.7				53	26.0				0.315[b]
Preexisting hypertension	50	82.0				140	68.6				0.042*,b
Venous insufficiency	3	4.9				6	2.9				0.455[b]
Arrhythmia	11	19.3				20	11.9				0.162[b]
Malignancy history	4	6.6				26	12.7				0.181[b]
Chronic anticoagulant use											
Warfarin	8	13.1				4	2.0				< 0.001*,b
Apixaban/rivaroxaban	3	4.9				14	6.9				0.587[b]
Acetylsalicylic acid	27	44.3				71	34.8				0.179[b]
Clopidogrel	5	8.2				18	8.8				0.879[b]
Chronic alcoholism	2	3.3				1	0.5				0.133[b]
Steroid use	4	6.6				4	2.0				0.066*,b
Tobacco use	9	14.8				37	18.1				0.540[b]

PWD, persistent wound drainage; SD, standard deviation; IQR, interquartile range; CCI, Charlson comorbidity index; ASA, American Society of Anesthesiologists; AO-OTA, Arbeitsgemeinschaft für Osteosynthesefragen/Orthopaedic Trauma Association; Hb, hemoglobin; NLR, neutrophil lymphocyte ratio; * variables with $p < 0.10$ were used in the stepwise backward multivariate logistic regression analysis; [a] Mann-Whitney U test; [b] Chi-square test; [c] Student's t-test.

TABLE II
Multivariate stepwise logistic regression analysis results of risk factors for persistent wound drainage after hip hemiarthroplasty surgery

Factor	β coefficient	SE	OR	95% CI	*p*
Postoperative day one albumin level	-0.157	0.039	0.85	0.79-0.92	<0.001
Preexisting hypertension	0.915	0.393	2.50	1.15-5.39	0.020
Chronic preoperative warfarin use	2.099	0.667	8.15	2.20-30.14	0.002

SE, standard error; OR, Odds ratio; CI, confidence interval.

including apixaban/rivaroxaban, acetylsalicylic acid, and clopidogrel (p = 0.362, 0.587, 0.179, and 0.879, respectively). Similarly, chronic alcohol use, steroid use, and smoking were not significantly different between groups (p = 0.133, 0.066, and 0.540, respectively; Table I).

After the backward stepwise elimination process, nine variables were included in the multivariate logistic regression model: older age, left-side surgery, AO/OTA type 31A fracture type, lower admission hemoglobin, lower admission albumin, lower postoperative Day 1 albumin, preexisting hypertension, congestive heart failure, and chronic warfarin use. Among these, three were identified as independent predictors of PWD: lower postoperative Day 1 albumin level (odds ratio [OR] = 0.85; 95% confidence interval [CI] 0.79-0.92; $p < 0.001$), preexisting hypertension (OR = 2.50; 95% CI 1.155.39; p = 0.020), and chronic warfarin use (OR = 8.15; 95% CI 2.20-30.14; p = 0.002) (Table II).

The ROC curve for the combined model (postoperative Day 1 albumin, preexisting hypertension, and chronic warfarin use) yielded an AUC of 0.727 (95% CI 0.648-0.807; $p < 0.001$), indicating good discriminative ability. The optimal threshold value for postoperative Day 1 albumin was 30.50 g/L (sensitivity: 60.7%; specificity: 76.5%; $p < 0.001$). The individual AUCs were 0.665 for postoperative Day 1 albumin (95% CI 0.579-0.751), 0.567 for preexisting hypertension (95% CI 0.488-0.646), and 0.556 for chronic warfarin use (95% CI 0.469-0.642) (Figure 2).

In-hospital mortality was significantly higher in the PWD group (16.4%) compared to the non-PWD group (5.9%) (p = 0.009). The mean length of hospital stay was also longer in the PWD group (17.7 ± 11.8 days, range: 5 to 60) than in the non-PWD group (7.4 ± 6.3 days, range: 5 to 73) ($p < 0.001$). Sacral decubitus ulcers were more frequent in the PWD group (26.2%) than in the non-PWD group (10.8%) (p = 0.003). Additionally, rates of superficial and deep surgical site infections were significantly higher in the PWD group ($p < 0.001$ and p = 0.003, respectively). Among the 16 patients with superficial infections, 15 were successfully treated with a single-session debridement during the same hospitalization, while one patient required two sessions. Of the four patients with deep infections, two underwent treatment with the debridement, antibiotics, and implant retention (DAIR) procedure. In the remaining two cases, a two-stage revision protocol was initially planned and an antibiotic spacer was inserted; however, due to the patients' poor overall condition, definitive revision surgery could not be performed. Other in-hospital

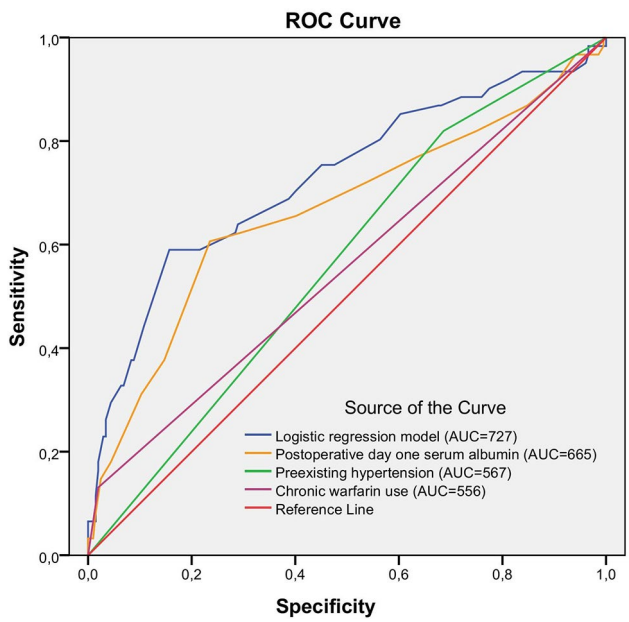


FIGURE 2. The ROC curves of the multivariate logistic regression model, postoperative Day 1 albumin (g/L), preexisting hypertension, and chronic warfarin use for predicting persistent wound drainage after hip hemiarthroplasty surgery. The logistic regression model was obtained from the multivariate analysis and consisted of these three identified predictive factors.
ROC, receiver operating characteristic; AUC, area under curve.

TABLE III
Clinical outcomes of the patients with and without persistent wound drainage

	PWD (n = 61)			Non-PWD (n = 204)			
Outcomes	n	%	Mean ± SD	n	%	Mean ± SD	*p*
In-hospital complications							
Acute kidney injury	6	9.8		7	3.4		0.052
Deep vein thrombosis	1	1.6		1	0.5		0.363
Pulmonary thromboembolism	2	3.3		4	2.0		0.544
Pneumonia	4	6.6		4	2.0		0.085
Gastrointestinal bleeding	2	3.3		1	0.5		0.133
Postoperative delirium	9	14.8		17	8.3		0.139
Sacral decubitus ulcer	16	26.2		22	10.8		0.003
Superficial wound infection	16	26.2		0	0		< 0.001
Deep wound infection	4	6.6		0	0		0.003
In-hospital death	10	16.4		12	5.9		0.009
Postoperative length of stay			17.7 ± 11.8			7.4 ± 6.3	< 0.001

PWD, persistent wound drainage; SD, standard deviation.

complications did not differ significantly between the two groups ($p > 0.05$). Detailed outcomes and complication rates are presented in Table III.

DISCUSSION

In the present study, we attempted to identify predictors of PWD in geriatric hip fracture patients treated with hemiarthroplasty and to evaluate its impact on in-hospital outcomes, including mortality, complications, and length of stay. We found that low postoperative Day 1 serum albumin level, preexisting hypertension, and chronic warfarin use were independent predictors of PWD. Moreover, patients with PWD experienced significantly higher in-hospital mortality, longer hospital stays, and more complications, including sacral decubitus ulcers and wound infections. Our findings highlight PWD as a major postoperative complication in geriatric hip fracture patients, with both local and systemic consequences. These results underscore the importance of identifying at-risk patients early and implementing targeted strategies to prevent PWD.

To the best of our knowledge, our study is the first to identify low postoperative Day 1 serum albumin levels as an independent predictor of PWD in elderly hip fracture patients treated with hemiarthroplasty. This result is consistent with previous research demonstrating the critical role of albumin in wound healing and overall patient recovery.[20,21] Albumin is a vital protein involved in maintaining oncotic pressure and transporting essential nutrients, and it acts as an acute-phase reactant. For these reasons, it is crucial for tissue repair and immune function.[22] Hypoalbuminemia is a frequent sign of malnutrition or systemic inflammatory conditions that are commonly seen in the elderly population and can impair these processes, leading to compromised wound integrity and prolonged exudation.[23] Previous studies have similarly demonstrated that low albumin level is a significant predictor for surgical site infections and other wound complications in orthopedic patients.[8,11,24] Furthermore, perioperative hypoalbuminemia has been found to be a significant predictor for wound complications following various surgical procedures.[11,25,26] In the light of these findings, early nutritional assessment and intervention, including albumin level monitoring, are crucial for geriatric hip fracture patients.[27,28] Proactive measures to optimize nutritional status both before and after surgery, such as dietary supplementation or intravenous albumin administration when indicated, could potentially mitigate the risk of PWD and enhance overall surgical results in this vulnerable patient group.[26,29]

The relationship between preexisting hypertension and PWD has rarely been directly investigated as a risk factor in previous studies. However, considering that hypertension can usually affect vascular integrity and tissue perfusion, its negative effects on wound healing may indirectly increase the risk of PWD.[30,31] Additionally,

fluctuations in blood pressure levels may lead to exudation, hematoma, and PWD. The finding that preexisting hypertension is an independent predictor for PWD in our study suggests that this comorbidity should be more closely monitored in geriatric hip fracture patients regarding wound drainage.[32,33] However, it should be noted that the statistical power for preexisting hypertension was relatively low (52.7%), which may limit the confidence in this association and suggests that larger studies may be needed to confirm this relationship.

We also found that chronic warfarin use significantly increased the risk of PWD. Anticoagulation therapy is known to impair hemostasis and promote hematoma formation, which can lead to prolonged wound leakage and increased infection risk.[34-36] While all patients in our cohort had their anticoagulants managed according to clinical guidelines, our findings suggest that warfarin users may require closer postoperative wound monitoring and adjusted anticoagulation strategies. More interestingly, other anticoagulants and antiplatelet agents were not significantly associated with PWD, which may reflect specific effects of warfarin or differing mechanisms of action of these agents.[37,38]

Our results also confirm the clinical impact of PWD on patient outcomes. We observed significantly higher rates of in-hospital mortality, prolonged hospitalization, and complications such as sacral decubitus ulcers and wound infections in the PWD group. These findings align with prior literature suggesting that PWD increases the risk of PJI, possibly through retrograde bacterial migration via the wound tract.[3,5] Prompt recognition and management of PWD may therefore be critical to preventing serious downstream complications, including deep infection and reoperation, and our data further show that not only were superficial and deep surgical site infections more frequent in the PWD group, but their management was also more complex. While most superficial infections could be controlled with limited surgical intervention, a considerable proportion of deep infections required advanced procedures such as DAIR or staged revision. Moreover, in two patients, definitive revision surgery could not be performed due to poor overall condition, underlining the particular treatment challenges faced in this population.

An important question is whether PWD should be considered a cause or a consequence of surgical site infections; several studies have shown that PWD is associated with an increased risk of periprosthetic/joint infection,[5,10] while narrative reviews and consensus statements emphasize that PWD can also be an early sign of an evolving infection and recommend clinical/serological evaluation to distinguish these scenarios.[3,17,39] Although our study was not primarily focused on the causal relationship between PWD and infection, we observed an association between the two. In certain patients, PWD may have been secondary to discharge associated with infection, whereas in others, retrograde bacterial migration may have occurred following PWD, subsequently leading to infection. A definitive causal relationship cannot be established from our data, and this issue warrants further investigation in future studies.

Nonetheless, this study has several limitations. First, although it was conducted in a single clinic to ensure a standardized surgical and perioperative treatment approach, its retrospective design may still introduce selection and information bias, and the findings cannot be generalizable to other settings, including different clinics within the same institution. Second, despite controlling for many variables, unmeasured confounders could still influence the results. Furthermore, the lack of a standardized definition for PWD complicates comparisons with previous studies. We used a pragmatic definition (> 2 cm^2 drainage beyond 72 h), in line with the recent literature, but universal criteria are still lacking. Additionally, the relatively low statistical power for preexisting hypertension increases the risk of type 2 error and suggests that the observed association may require validation in larger cohorts. Future multi-center, large-scale, prospective studies should aim to validate our findings and help establish standardized protocols for the prevention and management of PWD.

In conclusion, our study results showed low postoperative Day 1 serum albumin level, preexisting hypertension, and chronic warfarin use as independent risk factors for PWD in elderly patients undergoing hemiarthroplasty for hip fractures. In addition, PWD was associated with significantly increased in-hospital mortality, prolonged hospital stays, and higher rates of infection and decubitus complications. Early identification of patients at risk through albumin screening, assessment of comorbidities, and medication review may enable targeted interventions. Of note, nutritional optimization, such as dietary supplementation or intravenous albumin administration when indicated, careful perioperative blood pressure control, and close

monitoring of anticoagulated patients may help reduce the incidence of PWD and improve overall outcomes in this vulnerable patient group.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Participated in data collection, analysis, writing original draft, creating figures: Z.E.Ç.; Contributed to manuscript review and editing, creating figures, supervision: A.U.; Conducted material preparation, data collection: C.C.K.; Contributed to manuscript review and editing: O.B.; Contributed to study conception, manscript review and editing: B.Ö. All authors read and approved the final manuscript.

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