



## Evaluation of factors affecting the development of re-operation due to hemorrhage after lung resection

Yücel ÖZGÜR<sup>1,\*</sup>, Cemal AKER<sup>2</sup>

<sup>1</sup>Department of Anesthesiology and Reanimation, Bahçelievler Hospital, Istanbul, Turkey

<sup>2</sup>Department of Thoracic Surgery, Yedikule Chest Diseases and Thoracic Surgery Training and Research Hospital, Istanbul, Turkey

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### Abstract

In our study, preoperative factors affecting the development of re-operation after lung resection were examined. 413 patients who underwent lung resection between 2018-2020 were included in our study. The preoperative data of 25 (6.1%) patients who underwent re-operation and 388 (93.9%) patients who did not undergo re-operation were compared. Preoperative hemoglobin level ( $p=0.009$ ), neoadjuvant therapy ( $p<0.001$ ), pneumonectomy ( $p<0.001$ ), thoracotomy ( $p=0.005$ ), amount of intraoperative blood loss ( $p<0.001$ ), need for intraoperative blood product use ( $p=0.005$ ), intraoperative mean arterial pressure ( $p=0.01$ ), pulse rate ( $p=0.001$ ), postoperative hemoglobin amount ( $p<0.001$ ) were found to affect and increase the probability of re-operation. It was statistically significant that the need for postoperative blood product usage was higher ( $p<0.001$ ), postoperative complications (100% vs. 22.8%,  $p<0.001$ ) and mortality (0.6% vs. 4%,  $p=0.01$ ) in reoperated patients. It was found that the hospitalization day in the ICU was longer in those who underwent reoperation than in those who did not (3.2 days vs. 1.5,  $p<0.001$ ). Independent risk factors affecting re-operation according to multiple logistic regression analysis; neoadjuvant treatment ( $p<0.001$ ), operation time ( $p=0.04$ ), intraoperative pulse rate ( $p=0.01$ ) and postoperative hemoglobin ( $p<0.001$ ) were found. Low preoperative hemoglobin level, on the other hand, independently affected the development of re-operation at a level close to significance ( $p=0.06$ ). Re-operation due to bleeding after lung resection increases the rate of cardiopulmonary complications in the postoperative period. Careful follow-up and approach of surgery and anesthesia in the intraoperative period will contribute to the decrease in the incidence of re-operation.

**Keywords:** lung resection, re-operation, hemorrhage, lung cancer

### 1. Introduction

After lung resection, complications such as bleeding, bronchopleural fistula, persistent air leak, cardiac herniation, pulmonary torsion, empyema and lung ischemia may occur. 2-3% of these complications are bleeding (1-3). Although bleeding is a rare complication, it may cause hemodynamic instability and the need for aggressive treatment after surgery (4). The possibility of mortality and morbidity increases after re-operation.

While human error and technical problems come to the fore in surgical factors that cause hemorrhages, hemorrhage foci are the most common foci of the pulmonary artery, bronchial artery, intercostal artery and veins (4). In many studies, the bleeding focus cannot be determined exactly in the development of hemorrhage (1). Uramato and Litle have shown that factors such as the presence of lung cancer and the use of neoadjuvant and antiplatelet drugs were effective (4,5).

Our aim in this study was to evaluate the factors causing bleeding in patients who were re-operated for lung cancer.

### 2. Material and Methods

This study evaluated the demographic data, preoperative diagnosis, surgical procedure, intraoperative bleeding, mortality and morbidity of 25 (6.1%) patients who underwent re-operation due to hemorrhage among 413 lung resection patients operated between 2018-2021. No postoperative surgery was performed in 388 (93.9%) patients. The patients were evaluated in two groups as reoperated and non-reoperated. During this period, 324 (78.5%) thoracotomy and 89 (21.5%) VATS patients who were operated consecutively were included in the study. Lung cancer was diagnosed in 300 (72.6%) patients and benign lung mass was diagnosed in 113 (27.4) patients. The Ethics Committee of the Hospital approved this study. Confirmed number/date 2022-195/10.02.2022. The study was conducted in accordance with the Helsinki declaration principles. All patients signed a written consent form.

We recorded the preoperative data of the patients and used a standard general anesthesia protocol for all patients. We preoperatively administered antibiotic prophylaxis and used

propofol 2-3 mg/kg and fentanyl 2 µg/kg fentanyl for induction in all surgical procedures. We used 0.5 mg/kg intravenous (i.v.) rocuronium bromide as a muscle relaxant. We placed a double-lumen endobronchial tube on the right or left as appropriate, confirmed its position by fiberoptic bronchoscopy (FBS) and maintained anesthesia with 50% oxygen, 50% air, and 2% sevoflurane. We continued remifentanyl iv infusion throughout the operation. We determined the surgical procedure according to current guidelines for pneumonectomy and lobectomy and performed resections via thoracotomy or video-assisted thoracoscopic surgery (VATS).

We followed the bleeding status with preoperative arterial blood gas and hemogram tests and recorded the amount of blood in the aspirator, sponge and compresses at periodic intervals. We performed intraoperative 8 g/dl hemoglobin or 24% hematocrit. We administered no other blood product (aprotinin, factor VII or others) other than ES and fresh frozen plasma (FFP). After the operation, we transferred the patients who underwent pneumonectomy and lobectomy to the surgical intensive care unit. After one day of standard follow-up, we transported the patients who did not have hemodynamic instability to the recovery room. We arranged the management of patients using anticoagulant therapy before surgery; we discontinued antiplatelets such as warfarin three days and acetylsalicylic acid and clopidogrel seven days before the procedure. For patients undergoing coronary procedures (e.g., angioplasty, stenting), we contacted their cardiologist before discontinuing antiplatelet therapy and planned their treatment according to the nature of the planned surgery (elective or emergency). We initiated enoxaparin sodium routinely at a dose of 30 to 40 mg/day subcutaneously for prophylaxis before the scheduled surgery, unless the procedure was brief or the patient was young. We started enoxaparin sodium regardless of the patient's age if lung resection was planned. Intensive care specialists, intensive care nurses, and thoracic surgery assistants routinely monitored drainage and hemodynamic parameters. We included in the revision patients who continued to drain 100 mL for 8 hours or 200 mL for 2-4 hours and did not respond to medical treatment. We decided on one of the available treatment options according to the color, density, amount, laboratory values of the postoperative drainage, and the patient's hemodynamic status. Those options were primarily medical therapy, re-operation, hemorrhage-stopping therapy, blood product replacement and fluid therapy. We decided to operate considering the patient's hemodynamic data, x-ray, and the amount of hemorrhagic drainage. Considering the patient's bleeding status and hemodynamic stability, open thoracotomy was often preferred.

We performed surgeries 4-6 weeks after neoadjuvant therapy, as neoadjuvant chemotherapy and radiotherapy would increase postoperative hemorrhage.

Pulmonary complications were collected under pneumonia, acute respiratory failure, pulmonary embolism, prolonged air leak and need for mechanical ventilation. Cardiac complications were collected under the headings of arrhythmias, hemodynamic instability, acute coronary disease, angina, heart failure (HF) and thromboembolism.

### 2.1. Statistical analysis

We entered patient demographics and collected data into IBM® SPSS® (the Statistical Package for the Social Sciences) Statistics version 23 and characterized variables using mean, maximum, and minimum values while using percentage values for qualitative variables. We determined whether the distribution was normal or not by the Kolmogorov-Smirnov test and reported normal distributions as mean±SD. We used the student's t-test to compare groups, the Pearson chi-square test to analyze qualitative variables, and the Fisher's exact test if the group was small. We recorded non-parametric continuous variables as median and interval distribution and compared them using the Mann-Whitney U test. We considered a value of  $p < 0.05$  statistically significant and conducted multiple logistic regression analyses to determine the independent risk factors affecting re-operation. The multiple logistic regression analysis determined independent risk factors using only the variables that significantly increased the probability of re-operation in the univariate analysis,  $p < 0.05$ .

### 3. Results

With a mean age of 57.7 years (min=17, max=94 years), 76.8% of the patients were male, and 23.2% were female. Table 1 shows the patients' demographic, preoperative clinical and postoperative conditions. 155 (37.5%) of the patients had hypertension (HT), 82 (19.9%) diabetes mellitus (DM), 19 (4.6%) congestive heart failure (CHF), 80 (19.4%) chronic obstructive pulmonary disease (COPD), 79 (19.1%) coronary artery disease (CAD), 5 (1.2%) chronic kidney failure (CRF), 24 (5.8%) arrhythmias, 22 (5.3%) thyroid disease, and 8 (1.9%) cerebrovascular disease (CVO). Furthermore, 234 (56.7%), 113 (27.4%) and 27 (6.5%) had a history of smoking, anticoagulation and neoadjuvant therapy, respectively. No statistically significant correlation was present between the preoperative chronic diseases of the patients and the re-operation.

We used at least one blood product in 24.5% (n=101) and postoperatively in 16.9% (n=70) of the patients. While the number of patients who used at least 1 unit (U) of erythrocytes intraoperatively was 87 (21.1%), 59 (14.3%) used at least 1 U of erythrocytes postoperatively. 185 (20.6%) used at least 1 U fresh frozen plasma (FFP) intraoperatively, while the number of patients who used at least 1 U FFP postoperatively was 43 (10.4%). We used an average of 1.4 U ES and 1.0 U ES in those who underwent Thoracotomy and VATS, respectively. We used an average of 1.7 U ES in pneumonectomies and 1.2 U ES in lobectomies patients in the

intraoperative period and applied medical treatment to 100 (24.2%) postoperatively, and it was successful in 75% of these patients.

**Table 1.** Demographic, preoperative clinical and postoperative status of the patients

Variable	Data
Age, Year±SD	57.7±13.1
Gender, n (%)	
Male	317 (76.8%)
Female	96 (23.2%)
Diagnosis, n (%)	
Lung cancer	300 (72.6%)
Lung mass	113 (27.4%)
Disease Localization, n (%)	
Right	239 (57.9%)
Left	174 (42.1%)
Preoperative hemoglobin, mg/dl ±SD	13.1±1.6
Anjio Bypass, n (%)	40 (9.7%)
Anticoagulant, n (%)	113 (27.4%)
Neoadjuvan, n (%)	27 (6.5%)
Resection type, n (%)	
Lobectomy	297 (71.9%)
Pneumonectomy	73 (17.7%)
Wedge Rzk	43 (10.4%)
Operation type, n (%)	
Thoracotomy	324 (78.5%)
VATS	89 (21.5%)
Operation time, hour±SD	3.9±0.7
Intraoperative blood loss, ml±SD	367.6±332.9
Intraoperative blood product use, n (%)	101 (24.5%)
Intraoperative MAP, mmHg±SD	66.1±11.7
Intraoperative heart rate, n/dk±SD	67.4±11.3
Postoperative blood product use, n (%)	70 (16.9%)
Postoperative hemoglobin, mg/dl ±SD	11.6±1.7
Re-Operation, n (%)	25 (6.1%)
Postoperative complication, n (%)	116 (28.1%)
Mortality, n (%)	5 (1.2%)
ICU length of stay, days±SD	1.8±9.8

ICU: intensive care unit.MAP: mean arterial pressure

25 (6.1%) of the postoperative patients required re-operation. Preoperative hemoglobin level (p=0.009), neoadjuvant therapy (p<0.001), pneumonectomy (p<0.001), thoracotomy (p=0.005), intraoperative blood loss amount (p<0.001), intraoperative blood product use (p=0.005), intraoperative mean arterial pressure (p=0.01), pulse rate (p=0.001) and postoperative hemoglobin amount (p<0.001) increased the reoperation rate. (Table 2). It was statistically significant that the need for postoperative blood product usage (p<0.001), postoperative complications (100% vs 22.8%, p<0.001) and mortality (0.6% vs 4%, p=0.01) were higher in reoperated patients. We found that the hospitalization day in the ICU was longer in those who underwent re-operation (3.2 days vs 1.5, p<0.001).

Independent risk factors affecting re-operation according to multiple logistic regression analysis were neoadjuvant therapy (odds ratio=5.882, 95%CI: 2.344-14.727, p<0.001), operation time (per hour, odds ratio=1.662, 95%CI: 0.982-2.813, p=0.04), intraoperative pulse rate (per unit increase, odds ratio=1.039, 95%CI:1.006-1.074, p=0.01) and postoperative hemoglobin (per unit decrease, odds ratio=1.996, 95%CI:1.474-2.702, p<0.001). Preoperative hemoglobin, on the other hand, affected the development of re-operation independently at a level close to significance (p=0.06) (Table 3).

**Table 2.** Factors affecting re-operation and the situation in postoperative follow-up between patients who required and did not require re-operation

Variable	Non-HNP (n=388)	HNP (n=25)	p-value
<i>Factors affecting re-operation</i>			
Age, year±SD	57.5±12.9	59.8±16.3	0.340
Gender, n (%)			0.170
Male	295 (76.1%)	22 (88 %)	
Female	93 (23.9%)	3 (12%)	
Diagnosis, n (%)			0.591
Lung cancer	283 (73%)	17 (68%)	
Lung mass	105 (27%)	8(32%)	
Disease localization, n (%)			0.125
Right	243 (63%)	20 (40%)	
Left	145 (37%)	15 (60%)	
Preoperative hemoglobin, mg/dl ±SD	13.2±1.6	12.5±1.3	<b>0.009</b>
Anjio Bypass, n (%)	59 (9.3%)	4 (9.5%)	1.000
Anticoagulant, n (%)	173 (27.2%)	9 (21.4%)	0.417
Neoadjuvan, n (%)	34 (5.3%)	12 (28.6%)	<b>&lt;0.001</b>
Resection type,n (%)			<b>&lt;0.001</b>
Wedge Rzk+lobectomy	328 (85%)	22 (48%)	
Pneumonectomy	60 (15%)	13 (52%)	
Operation type, n (%)			<b>0.005</b>
Thoracotomy	300(77.8%)	24 (95.9%)	
VATS	88 (22.6%)	1(4.1%)	
Operation time, hour±SD	3.8±0.7	4.5±0.7	<b>&lt;0.001</b>
Intraoperative blood loss, ml±SD	334.6±309.8	544.2±379.0	<b>&lt;0.001</b>
Intraoperative blood product use, n (%)	90 (23.1%)	11 (44%)	<b>0.019</b>
IntraoperativeMAP, mmHg±SD	66.5±11.0	62.1±11.2	<b>0.012</b>
Intraoperative heart rate, n/min±SD	67.1±10.4	74.8±14.0	<b>0.001</b>
<i>The situation in postoperative follow-up between patients requiring and not requiring re-operation</i>			

Postoperative blood product use, n (%)	48 (12%)	22 (88 %)	<0.001
Postoperative hemoglobin, mg/dl ±SD	11.7±1.7	10.1±1.4	<0.001
Postoperative complication, n (%)	91 (23%)	25 (100.0%)	<0.001
Postoperative respiratory complication	32 (8%)	8 (32%)	<0.001
Postoperative cardiac complication	82 (21%)	25 (100%)	<0.001
ICU length of stay, days±SD	1.5±7.9	3.2±2.7	<0.001
Mortality, n (%)	24 (0.6%)	1 (4%)	0.01

MAP: mean arterial pressure; VATS: Video-Assisted Thoracic Surgery; ICU: intensive care unit. Bold p-values indicate significant differences. HNP:

Postoperative complications were present in 116 (28%) patients, while 5 (1.2%) patients died postoperatively. Pulmonary complications developed in 40 (9.6%) patients, cardiac complications in 107 (25.9%), acute renal failure (ARF) in 11 (1.6%) and CVO in 2 (0.3%). The mean length of stay in the ICU was 1.6 days (min=1, max=200 days). As

pulmonary complications, 20 (4.8%) patients had acute respiratory failure, 15 (3.6%) pneumonia, 2 (0.5%) air leak, 4 (1%) pulmonary edema. As cardiac complications, hemodynamic instability was observed in 52 (12.6%), arrhythmia in 48 (11.6%), angina in 6 (1.4%) and asystole in 5 (1.2%) patients.

**Table 3.** Evaluation of factors affecting rethoracotomy by multiple logistic regression analysis

	Odds ratio	95% CI	p-value
Preoperative hemoglobin (per unit drop)	1.292	0.987-1.690	0.06
Neoadjuvan (No etc Yes)	5.882	2.344-14.727	<0.001
Resection type (Wedge+Lob. etc Pneumonectomy)	1.374	0.812-2.322	0.235
Type of operation (Thoracotomy etc VATS)	0.340	0.074-1.681	0.185
Operation time (per hour)	1.662	0.982-2.813	0.049
Intraoperative blood loss (per ml)	1.001	0.998-1.009	0.804
Intraoperative blood product use (No etc Yes)	0.818	0.298-2.246	0.697
Intraoperative MAP (per mmHg)	0.997	0.961-1.035	0.892
Intraoperative heart rate (per beat)	1.039	1.006-1.074	0.01
Postoperative hemoglobin (per unit drop)	1.996	1.474-2.702	<0.001

CI; confidence interval, Bold-signed p-values show significant differences.

Table 4 shows the relationship between postoperative general and respiratory and cardiac complications, and the amount of intraoperative blood loss and intraoperative blood product use. We found that both the amount of intraoperative blood loss and the use of at least one intraoperative blood product were associated with general postoperative

complications and respiratory and cardiac complications.

In the ROC analysis for re-operation, we observed a better capacity for prediction of APACI (AUC: 0.884, 95% CI: 0.842-0.927, p<0.001) and SOFA (AUC: 0.892, 95% CI: 0.837-0.948, p<0.001) scores compared to the ASA score.

**Table 4.** The relationship between general postoperative complication, respiratory and cardiac complications, and the amount of intraoperative blood loss and intraoperative blood product use

	Amount of intraoperative blood loss, ml±SD	p-value	Intraoperative blood product use (n=101), n (%)	p-value
Postoperative general complication, n (%)				
no (n=297)	320.4±325.5	<0.001	49 (16.4%)	<0.001
yes (n=116)	486.2±322.9		52 (44.8%)	
Postoperative respiratory complication n (%)				
no (n=373)	347.4±323.3	<0.001	80 (21.4%)	<0.001
yes (n=40)	546.5±369.9		21 (51.6%)	
Postoperative cardiac complication n (%)				
no (n=306)	329.1±330.0	<0.001	54 (17.6%)	<0.001
yes (n=107)	475.3±318.5		47 (43.9%)	

SD; standard deviation, Bold p-values indicate significant differences

#### 4. Discussion

In this study, we examined the relationship between re-operation after lung resection and the preoperative data of the patients and determined the presence of neoadjuvant for re-operation, prolonged operation time and increased

intraoperative pulse rate as independent risk factors.

Re-operation after thoracic surgery is frequently applied for postoperative bleeding (1-5). Bleeding complications after lung resection vary between 2-3%, but this rate can reach up

to 6-13.5% in completion pneumonectomies. Although the incidence of re-operation after bleeding is not common, it is 2-3% and 1% after open and VATS, respectively (4). We found the re-operation rate as 6.1% on average, consistent with the literature.

Miyazaki et al. found no correlation between intraoperative bleeding and morbidities in their study of 241 patients who underwent VATS (2). Uramoto et al. showed that there was no correlation between hemorrhage after lung cancer surgery and patients' age, gender, smoking, clinical stage, pathological stage, and histology (4). However, Nakamura et al. found a correlation between intraoperative bleeding and the operating procedure, gender, disease stage, and histologic type (6). Decaluwe et al. revealed a relationship between chemotherapy and major intraoperative complications (7). In parallel with the literature, we found neoadjuvant therapy to be among the independent risk factors for re-operation. In addition, we found no significant relationship between the chronic diseases of the patients and the re-operation.

Perioperative bleeding is lower in VATS patients than in open thoracotomy because VATS patients represent a select group with more peripheral, smaller and safer lesions for resection. Erdogu et al. observed the re-operation rate as 3.3% after thoracotomy and 0.4% after VATS (8). In the literature, postoperative hemorrhage was observed as 2-3% after thoracotomy and 1.7% after VATS. In our study, 95.2% of the patients who underwent re-operation were patients who underwent thoracotomy. We performed re-operation in 8% of those who underwent thoracotomy and 1.1% of those who underwent VATS.

Harpole et al. found the re-operation rate as 2.9% after lobectomy and 3% after pneumonectomy (9). Erdogu et al. found this rate as 11.5% in pneumonectomies and 1.7% in lobectomies (8). Our study found pneumonectomy to be among the independent risk factors for re-operation. We performed re-operation in 3.8%, 21% and 2.3% of those who underwent lobectomy, pneumonectomy, and wedges, respectively. In their study examining 27 patients who were reoperated, Sayar et al. found that pneumonectomy was the primary operation of 59.9% of the patients who underwent re-operation (1). In our study, that rate was 52%.

Factors such as technical problems (70-80%), hemodilution, hypothermia, depletion of coagulation factors (DIC) and acidosis seem to be responsible for bleeding due to surgery. Studies have shown that the possibility of postoperative complications and mortality increases in intraoperative bleedings >250 ml in patients who underwent surgery (10, 11). Yano et al. found the average intraoperative bleeding rate as 186 and 856 ml in patients who underwent lung resection and re-operation, respectively (12). In our study, the mean intraoperative blood loss was 367 ml, while it was 547 ml in those who underwent re-operation and 334 ml

in those who did not. Studies have shown a relationship between intraoperative bleeding >100 ml in patients undergoing lung resection with VATS and postoperative cardiopulmonary complications, prolonged chest tube length of stay, and prolonged hospital stay (13). In their extensive retrospective study, Li et al. revealed massive bleeding in patients who underwent thoracic surgery as the leading cause of mortality (14). Nakamura et al. showed that intraoperative bleeding >381 ml in patients undergoing resection for lung cancer was an independent risk factor for patients' survival (6). The average amount of intraoperative bleeding in patients undergoing VATS resection was in the range of 100-400 ml (13). Our study revealed 259 ml of bleeding in patients who underwent VATS and 396 ml in those who underwent thoracotomy. These results are compatible with the literature.

Studies have shown that increased intraoperative heart rate (>87 beats/min) and decreased mean arterial pressure were associated with impaired myocardial function and increased incidence of mortality in patients undergoing surgery (15). Increased heart rate decreases coronary blood flow, increases myocardial oxygen requirement and causes myocardial damage. As a result of volume loss due to bleeding, decreased oxygen supply to vital organs, immune suppression, and pulmonary edema may occur due to excessive fluid overload (13). Brady et al. found a correlation between values of <55-75 mmHg for MAP and an increased incidence of postoperative acute renal failure and MI (16). Our study revealed a correlation between increased pulse rate and decreased MAP and re-operation, and postoperative cardiopulmonary complications.

A study of 3500 patients who underwent lung resection observed bleeding requiring the use of >4 U ES in 2.9% of lobectomies and 3% of pneumonectomies (5). We used in our study an average of 1.7 U ES in pneumonectomies and 1.2 U ES in lobectomies patients in the intraoperative period. Undesirable side effects may occur in patients undergoing surgery for lung cancer due to perioperative bleeding due to blood transfusion. As the amount of blood product used increases, the rate of complications such as postoperative respiratory failure, infection, and acute kidney failure increases (17-19). Thomas et al. found that the patient's age, neoadjuvant therapy, pneumonectomy and prolonged operation time were independent risk factors for blood transfusion in thoracic surgery. The same study also evinced that intraoperative >2 U ES blood transfusion increased 30-day mortality by two times (18). We found in our study a relationship between blood transfusion and postoperative respiratory and heart failure.

In this study, we examined the relationship between re-operation after lung resection and the perioperative data of the patients and determined neoadjuvant for re-operation, prolonged operation time, increased intraoperative pulse rate as independent risk factors. Rapid diagnosis and treatment of

hemorrhages that develop due to lung resection and require re-operation significantly affected mortality and morbidity. Careful observation of the markers of perioperative hemorrhage and close patient follow-up with the cooperation of clinical branches would decrease the incidence of hemorrhage-related mortality and morbidity.

This study had two limitations. Firstly, we conducted the study in a single center and retrospectively. Secondly, since our hospital is a training and research hospital with more than one clinical branch, there is a high probability of different approaches in surgery.

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The Ethics Committee of the Hospital approved this study. Confirmed number/date 2022-195/10.02.2022. The study was conducted in accordance with the Helsinki declaration principles. All patients signed a written consent form.

#### Conflict of interest

The authors declared that there was no conflict of interest during the preparation and publication of this article.

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#### Authors' contributions

Concept: Y.Ö., Design:Y.Ö., C.A., Data Collection or Processing:Y.Ö., C.A., Analysis or Interpretation: Y.Ö., C.A., Literature Search: Y.Ö., Writing: Y.Ö.

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