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The Effect of Homocysteine Levels on Thrombolytic Treatment in Acute Ischemic Stroke

Akut İskemik İnmede Homosistein Düzeyinin Trombolitik Tedavi Üzerine Etkileri

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Abstract

Objective: Hyperhomocysteinemia is an independent risk factor for cardiovascular diseases. It has paradoxically both antifibrinolytic and pro-hemorrhagic effects. In the study, we investigated the effect of homocysteine (Hcy) levels on thrombolytic therapy in patients with acute ischemic stroke.

Materials and Methods: Patients who received intravenous (iv) tissue plasminogen activator (tPA) between 2005 and 2021 and had Hcy levels measured within the first 3 days were reviewed in terms of tPA efficacy, prognosis and intracerebral hemorrhage. The efficacy of tPA treatment was categorized as effective response (decrease of at least 4 points or a decrease in score to zero) and dramatic response (decrease of at least 8 points or a decrease in score to either zero or one) according to NIHSS score at 24 hours. Scores of 0 and 1 were classified as "excellent outcome", and scores of 0, 1, and 2 were classified as "good outcome" on the modified Rankin scale evaluated at 3 months. Hemorrhagic transformation was evaluated according to Fiorelli's classification.

Results: Effective response was observed in 46.7% of the 182 patients (mean age 71±14 years; 99 women) included in the study, and dramatic response in 31.3%. Excellent outcome was reported in 33% of the patients, and good outcome in 53.3%. Cerebral hemorrhage of any severity was detected in 15.9% of the patients, and parenchymal hematoma type 2 in 5.5%. In the analyses made for assessing iv tPA response and cerebral hemorrhage status, no difference was found in terms of Hcy level and between the subgroups formed with different cut-off values of Hcy level.

Conclusion: In our study, hyperhomocysteinemia, which is known to have negative effects on fibrinolysis and vascular integrity, did not show a significant effect on iv tPA efficacy, prognosis and complications. Prospective and large-sample sized studies are needed to better demonstrate these effects.

Keywords: Homocysteine, tissue plasminogen activator, acute ischemic stroke

Öz

Amaç: Hiperhomosisteinemi, kardiyovasküler hastalıklar açısından bağımsız bir risk faktörüdür. Hem antifibrinolitik hem de kanama eğilimine neden olabilecek etkileri vardır. Çalışmamızda, akut iskemik inmede trombolitik tedavi üzerine etkileri incelendi.

Gereç ve Yöntem: Çalışmada, 2005-2021 yılları arasında hastanemizde intravenöz (iv) doku plazminojen aktivatörü (tPA) tedavisi alan ve 3 gün içinde bakılmış homosistein (Hcy) düzeyi olan hastalar tPA etkinliği, prognoz ve intraserebral kanama açısından değerlendirildi. iv tPA tedavisi etkinliği, 24. saat NIHSS skorunda azalma durumuna göre etkin cevap (en az 4 puan azalma veya skorun sıfır olması) ve dramatik cevap (en az 8 puan azalma veya skorun sıfır ya da bir olması) olarak kategorize edildi. Üçüncü ayda değerlendirilen modifiye Rankin skalasına göre 0 ve 1 puan "mükemmel sonlanım"; 0, 1 ve 2 puan "iyi sonlanım" olarak sınıflandırıldı. iv tPA sonrası serebral kanama sınıflandırması için kontrastsız beyin bilgisayarlı tomografide (BT) Fiorelli's sınıflaması kullanıldı.

Bulgular: Çalışmaya dahil edilen 182 hastanın (yaş ortalaması 71±14 yıl; 99 kadın) %46,7'sinde etkin cevap, %31,3'ünde dramatik cevap izlendi. Hastaların %33'ünde mükemmel sonlanım, %53,3'ünde iyi sonlanım görüldü. iv tPA sonrası kontrol beyin BT'de hastaların %15,9'unda herhangi bir şiddette serebral kanama, %,5,5'inde parankimal hematom tip 2 tespit edildi. Prognoz, tPA cevabı ve tPA sonrası serebral hemoraji durumuna göre yapılan analizlerde Hcy düzeyi ve farklı kesim değerleri ile oluşturulan subgruplar arasında bir farklılık saptanmadı.

Sonuç: Çalışmamızda, fibrinolizis ve vasküler bütünlük üzerine negatif etkileri olduğu bilinen hiperhomosisteineminin iv tPA etkinliği, prognozu ve komplikasyonları üzerine belirgin bir etkisi gösterilememiştir. Bu etkilerin daha iyi ortaya konulabilmesi için prospektif ve geniş katılımlı çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Homosistein, doku plazminojen aktivatörü, akut iskemik inme

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Introduction

Homocysteine (Hcy) is a sulfur amino acid that does not take part in the protein structure and is located at the intersection of re-methylation and trans-sulfuration metabolic pathways. It plays a role in the synthesis of S-adenosine methionine (general methyl donor in methylation reactions), methionine, cysteine, alpha-ketobutyrate and taurine (1). It also plays a role in reactions in which vitamin B12, folic acid and pyridoxine are co-enzymes. If its level is above 15 µmol/l, it is defined as hyperhomocysteinemia. According to the plasma Hcy level; it is classified as mild hyperhomocysteinemia between 16-30 µmol/l, moderate between 31-100 µmol/l and severe over 100 µmol/l (2). Hyperhomocysteinemia can be observed frequently due to genetic and environmental (vitamin deficiencies, kidney failure, thyroid dysfunction, cancer, psoriasis, diabetes, alcohol, smoking, advanced age, menopause, etc.) factors (3).

Hyperhomocysteinemia is an independent risk factor for cardiovascular diseases (4). Hcy causes oxidative stress, calcium entry into the cytoplasm, induction of cell apoptosis and endothelial dysfunction by binding to the N-methyl-D-aspartate receptor, an excitatory neurotransmitter. It triggers phagocytes to form foam cells by reacting with apoB parts of lipoproteins (3,5,6). Elastolysis mediated by metalloproteinases in the arterial wall is induced at high Hcy levels. Deteriorated vascular integrity is associated with hemorrhagic complications (7,8). Increased Hcy in plasma is converted to homocysteine-thiolactone, a potent oxidant. Homocysteine-thiolactone causes oxidative changes on plasma proteins such as fibrinogen (9). It has been shown that the microscopic structure of Hcy-associated fibrin fiber is different from the controls and it has a short, thick and more branched compact structure. This change in fibrin fibers complicates fibrinolysis (10).

The efficacy of intravenous (iv) tissue plasminogen activator (tPA) treatment has been demonstrated in acute ischemic stroke (AIS) and it is routinely applied in appropriate patients (11). In our study, we evaluated the effect of plasma Hcy level on the efficacy and prognosis of iv tPA treatment and the complications of cerebral hemorrhage that may develop after treatment.

Materials and Methods

Among the 263 patients who received iv tPA treatment without mechanical thrombectomy, who were hospitalized and evaluated in our hospital between the years 2005 and 2021; 182 (mean age 71±14 years; 99 women) patients with Hcy levels measured in the first 3 days were evaluated in terms of tPA efficacy, prognosis, and intracerebral hemorrhage. Age, gender, stroke risk factors, stroke etiology, length of stay, admission National Institutes of Health Stroke Scale (NIHSS) score, 24th hour NIHSS score, symptom onset-tPA onset time (min), and 3rd month modified Rankin scale (mRS) score were recorded in a prospectively created stroke database. Plasma Hcy, mean corpuscular volume (MCV), folic acid and vitamin B12 levels of the patients were analyzed retrospectively. Ethical approvals were obtained from the Hacettepe University Non-Invasive Clinical Research Ethics Committee for the stroke database and the project (decision no: 2022/07-48, date: 19.04.2022).

Etiology of stroke was evaluated according to the "Causative Classification of Stroke System (CSS)" stroke classification (12). Stroke severity was measured with the NIHSS score (13). The NIHSS score was measured at the time of admission, at the 24th hour of iv tPA treatment, and at discharge. Disability was determined by the mRS score (14) measured at the 3rd month. The efficacy of iv tPA treatment was assessed by measuring the reduction in the NIHSS score at 24 hours compared to admission. Accordingly, a decrease of at least 4 points in the NIHSS score or a zero NIHSS score at the 24th hour was considered an effective response. A dramatic response was defined as a decrease of at least 8 points in the NIHSS score or a NIHSS score of 0 or 1 at 24 hours. Analyses were performed between the groups with and without an effective response, and between the groups with and without a dramatic response. Effective response and dramatic response groups were not compared with each other. At 3 months, mRS scores of 0 and 1 were classified as "excellent outcome" and mRS scores of 0, 1 and 2 were classified as "good outcome" (15,16).

Cerebral hemorrhage after iv tPA treatment was evaluated according to the Fiorelli classification in the control non-contrast brain computed tomography (CT) performed at 24-36 hours. Since the parenchymal hematoma-2 (PH-2) category was associated with early neurological deterioration and 3-month mortality, patients in this category were analyzed separately in the study (17).

Statistical Analysis

Analyses were performed with SPSS version 22. All data were expressed as mean ± standard deviation, median (min-max), mean (95% confidence interval), or percentage according to their characteristics. The normal distribution was evaluated with Kolmogorov-Smirnov test for effective response, dramatic response, excellent outcome, and good outcome groups with a sample size greater than 50. Shapiro-Wilk test was used to evaluate the normal distribution for the groups with a sample size of less than 50 in the cerebral hemorrhage and PH-2. Mann-Whitney U for numerical variables and chi-square/Fisher's exact test was used for categorical variables, since the data did not show normal distribution in evaluating the difference between groups. $P<0.05$ was considered statistically significant.

Results

Etiologies of stroke according to CSS in 182 patients included in the study were as follows: Cardioembolism in 31.3%, cryptogenic embolism in 30.2%, cryptogenic stroke in 14.3%, small vessel disease in 6.6%, large vessel atherosclerosis in 6.6%, stroke of undetermined etiology in 5.5%, insufficient investigation in 3.8% and stroke of other determined etiology in 1.6%. Median (min-max) serum Hcy level of the patients was 14.2 (2.2-200) µmol/l, MCV was 86.8 (59.8-108.9) fL, folic acid level was 8.7 (1.9-24.8) µg/l and vitamin B12 level was found to be 189 (19-1179) ng/l. High Hcy levels were observed in 45.6% of the patients. The median Hcy level was 15.4 (2.3-41) µmol/l in patients with cardioembolism, 13.2 (2.2-110) µmol/l in patients with cryptogenic embolism, 13.5 (5.8-36.2) µmol/l in patients with cryptogenic stroke), 13.2 (6.8-37.5) µmol/l in patients with small vessel disease, 13 (6.6-200) µmol/l in patients with large vessel atherosclerosis, 13.8 (11.2-23.3) µmol/l in patients with stroke of undetermined etiology, 12.7 (9.2-29.8) µmol/l in those with insufficient research, and 10.6 (6-21.2) µmol/l in those with stroke due to other causes. No statistically significant difference was observed in Hcy levels according to stroke etiology.

An effective response was observed in 46.7% of the patients and a dramatic response was observed in 31.3% of the patients with intravenous thrombolysis (IVT). The time between symptom onset and administration of IVT was statistically significantly shorter, and the frequency of cerebral hemorrhage and the length of hospital stay were statistically significantly lower in the effective response group. In the dramatic response group, the frequency of cerebral hemorrhage and length of hospital stay, as well as the frequency of hypertension, were found to be statistically significantly lower. Although Hcy level was lower in those with effective and dramatic responses, no statistically significant difference was found between groups formed with Hcy level and its different cut-off values in terms of effective response and dramatic response (Table 1).

Excellent outcome was observed in 33% of the patients, and good outcome was observed in 53.3% of the patients. Age, NIHSS score at admission, frequency of cerebral hemorrhage, and length of hospital stay were statistically significantly lower in the excellent outcome and good outcome groups. In addition, the frequency of hypertension in the excellent outcome group was also found to be statistically significantly lower. There was no statistically significant difference in terms of excellent outcome and good outcome according to the groups formed with Hcy level and its different cut-off values (Table 2).

In the control brain CT after IVT, cerebral hemorrhage of any severity was detected in 15.9% of the patients and PH-2 in 5.5% of the patients. Although the length of hospital stay was statistically significantly longer in both groups, the frequency of atrial fibrillation and the NIHSS score at admission were also statistically significantly higher in patients with cerebral hemorrhage. No statistically significant difference was found in the cerebral hemorrhage and PH-2 groups according to the groups formed with Hcy level and its different cut-off values (Table 3).

Since there were studies in the literature suggesting that the effect of Hcy levels on prognosis was more pronounced in patients with thrombocytopenia, analyses were repeated in the group with thrombocytopenia (platelet count <159,000 cells/µl) (data not presented) (18). No statistically significant difference was observed in the efficacy of iv tPA, the prognosis of the patients, and the frequency of hemorrhage after iv tPA according to the presence of hyperhomocysteinemia.

Discussion

The potential effects of increased Hcy levels, which may cause both antifibrinolytic and bleeding tendency, are known. In a study conducted by measuring hemostatic risk factors in 3.216 participants without cardiovascular disease, it was shown that high Hcy level was associated with increased plasminogen activator inhibitor-1 and tPA antigen levels. This suggests that increased Hcy level is associated with deterioration in fibrinolytic potential (19). The effects of Hcy on the fibrin system are described through

Table 1. Response to intravenous tPA therapy

	Effective response			Dramatic response		
	Yes (n=85)	No (n=96)	p	Yes (n=57)	No (n=124)	p
Age	71±15	71±14	0.904	71±16	71±14	0.935
Female	58%	52%	0.453	63%	51%	0.121
BMI	27.6±5.4	27.3±4.8	0.902	28±5.8	27.1±4.6	0.585
HT	65.9%	77.1%	0.095	**59.6%**	**77.4%**	**0.014**
DM	27.1%	32.3%	0.443	22.8%	33.1%	0.161
AF	16.5%	19.8%	0.564	17.5%	18.5%	0.871
NIHSS score at admission	12±6	11±6	0.298	12±6	11±6	0.543
Symptom onset to tPA time (min)	**166±62**	**198±68**	**<0.001**	176±69	185±66	0.206
Presence of hemorrhage	**7.1%**	**24%**	**0.002**	**5.3%**	**21%**	**0.007**
Stay at hospital	**10±16**	**19±22**	**<0.001**	**11±18**	**17±21**	**<0.001**
Cardioembolism	41.3%	39.3%	0.826	42.5%	39.2%	0.732
Large vessel atherosclerosis	8.2%	5.2%	0.414	7%	6.5%	1
Small vessel disease	4.7%	8.3%	0.328	5.3%	7.3%	0.755
Hcy (µmol/l)	15.9±7.7	19.9±24.6	0.88	15.3±7.1	19.3±22.1	0.628
Hcy >15 µmol/l	42.4%	47.9%	0.453	38.6%	48.4%	0.219
Hcy >30 µmol/l	4.7%	8.3%	0.328	3.5%	8.1%	0.345
Hcy >100 µmol/l	0%	2.1%	0.499	0%	1.6%	1
Q4 (Hcy)	22.4%	25%	0.676	17.5%	26.6%	0.183
MCV (fL)	85.7±7.8	87±6.7	0.551	85.5±8.2	86.8±6.7	0.49
Folic acid (µg/l)	10.1±5.4	9.5±5.1	0.588	10±5.7	9.7±5	0.775
B12 vitamin (ng/l)	**267±184**	**224±148**	**0.032**	244±193	244±153	0.786

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation, NIHSS: National Institutes of Health Stroke Scale, tPA: Tissue plasminogen activator, Hcy: Homocysteine, MCV: Mean corpuscular volume, Q4: Homocysteine 4th quarter by level

Table 2. Prognosis

	Excellent outcome			Good outcome		
	Yes (n=60)	No (n=122)	p	Yes (n=97)	No (n=53)	p
Age	**65±16**	**75±12**	**<0.001**	**67±16**	**77±11**	**<0.001**
Female	53%	55%	0.840	51%	59%	0.262
BMI	28.5±5.2	27±5	0.275	28.3±5.9	26.4±3.8	0.164
HT	**58.3%**	**78.7%**	**0.004**	66%	78.8%	0.054
DM	25%	32.8%	0.282	26.8%	34.1%	0.284
AF	16.7%	18.9%	0.719	16.5%	20%	0.54
NIHSS score at admission	**9±6**	**13±6**	**<0.001**	**9±5**	**14±6**	**<0.001**
Symptom onset to tPA time (min)	174±68	187±66	0.275	177±61	189±72	0.302
Presence of hemorrhage	**8.3%**	**19.7%**	**0.049**	**9.3%**	**23.5%**	**0.009**
Stay at hospital	**7±5**	**19±23**	**<0.001**	**8±7**	**24±26**	**<0.001**
Cardioembolism	36.8%	42%	0.595	41.3%	39.3%	0.826
Large vessel atherosclerosis	6.7%	6.6%	1	5.2%	8.2%	0.403
Small vessel disease	8.3%	5.7%	0.534	8.2%	4.7%	0.337
Hcy (µmol/l)	15.5±6.8	19.3±22.3	0.709	18±20.3	18.1±16.9	0.761
Hcy >15 µmol/l	40%	48.8%	0.287	50.6%	49.4%	0.505
Hcy >30 µmol/l	3.3%	8.2%	0.342	6.2%	7.1%	0.813
Hcy >100 µmol/l	0%	1.6%	1	1%	1.2%	1
Q4 (Hcy)	21.7%	25.4%	0.579	25.8%	22.4%	0.591
MCV (fL)	85.5±7.5	86.8±7	0.215	85.8±7.3	87±7.1	0.411
Folic acid (µg/l)	9.7±4.7	9.9±5.5	0.955	10.1±5.1	9.5±5.4	0.418
B12 vitamin (ng/l)	252±197	240±149	0.927	244±191	243±131	0.329

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation, NIHSS: National Institutes of Health Stroke Scale, tPA: Tissue plasminogen activator, Hcy: Homocysteine, MCV: Mean corpuscular volume, Q4: Homocysteine 4th quarter by level

several mechanisms in the literature. Hcy inhibits the cell surface protein annexin A2 complex, which acts as a coreceptor for plasminogen and tPA. It has been shown that annexin A2 isolated from hyperhomocysteinemic mice cannot fully support tPA-dependent plasmin activation (20). High Hcy level leads to the formation of shorter, branched and compact fibrin fibers. Fibrin fibers of this structure are resistant to fibrinolysis (21,22,23,24). On the other hand, increased Hcy causes an increase in endothelial dysfunction and blood-brain barrier permeability in addition to these anti-fibrinolytic effects. For this reason, there is information in the literature that increased level of Hcy may also contribute to the hemorrhagic processes (7,25).

Despite these effects of high Hcy levels detected in animal studies and *in vitro* experiments, this interaction could not be clearly demonstrated in studies conducted in patients with AIS receiving thrombolytic therapy to examine the effect of Hcy levels on thrombolytic treatment. There were studies that associated hyperhomocysteinemia with a high NIHSS score, poor outcome, and symptomatic intracerebral hemorrhage. (26,27,28) In these studies with a similar sample size as our study, it was observed that the ratio of male sex, which was known to be associated with higher Hcy levels in all age groups, was significantly higher than our study (29). When the Hcy levels of the participants were compared, the mean ± standard deviation of the Hcy level was 22.62±21.23 µmol/l in a study (27) and 27.57±20.17 µmol/l in another study (26), whereas in our study, the median (min-max) of Hcy level was 14.2 (2.2-200) µmol/l, lower than the levels reported in these two studies. In these studies, it was observed that stroke severity and outcome parameters in different groups of Hcy levels were evaluated rather than evaluating hyperhomocysteinemia in patients with poor and good outcome, and mean NIHSS scores at baseline and at first week were used to measure the efficacy of thrombolytic therapy (26,27,28). There are common risk factors affecting both the severity of stroke and hyperhomocysteinemia. In these studies, the frequencies of risk factors such as smoking and diabetes mellitus were found to be higher in groups with high Hcy levels. As a matter of fact, in one of these studies, it was stated that the contribution of Hcy level to the outcome decreased when adjustment was made for the confounding factors (28). In a study evaluating the Hcy level before thrombolytic treatment, no relationship was found with recanalization and outcome (30). Unlike studies that associated high Hcy levels with cerebral hemorrhagic complications, symptomatic intracerebral hemorrhage (4 point increase in NIHSS score with hemorrhage or hematoma detected by CT) was evaluated in some other studies (26,27). In our study, the frequency of cerebral hemorrhage of any severity was 15.6%, while the frequency of symptomatic intracerebral hemorrhage was reported as 47.5% in one of these studies (26). There were also studies in the literature indicating that the Hcy level measured before thrombolytic therapy was not associated

Table 3. Intracranial hemorrhage after intravenous tPA

	Cerebral hemorrhage			Parenchymal hematoma type 2		
	Yes (n=29)	No (n=153)	p	Yes (n=10)	No (n=172)	p
Age	75±10	71±15	0.14	79±6	71±15	0.096
Female	59%	54%	0.618	50%	55%	1
BMI	26.1±4.5	27.7±5.2	0.385	26.3±2.4	27.5±5.2	0.903
HT	69%	72.5%	0.694	70%	72.1%	1
DM	37.9%	28.8%	0.324	40%	29.7%	0.493
AF	**34.5%**	**15%**	**0.013**	20%	18%	1
NIHSS score at admission	**14±6**	**11±6**	**0.036**	15±6	11±6	0.07
Symptom onset to tPA time (min)	188±44	182±70	0.27	182±32	183±68	0.818
Stay at hospital	**26±26**	**13±18**	**<0.001**	**40±40**	**14±17**	**0.002**
Cardioembolism	68.4%	35%	0.006	40%	40.4%	1
Large vessel atherosclerosis	0%	7.8%	0.219	0%	7%	1
Small vessel disease	0%	7.8%	0.219	0%	7%	1
Hcy (µmol/l)	16.3±16.3	18.4±19.2	0.074	18.6±24.8	18±18.4	0.104
Hcy >15 µmol/l	34.5%	47.7%	0.19	20%	47.1%	0.113
Hcy >30 µmol/l	6.9%	6.5%	1	10%	6.4%	0.504
Hcy >100 µmol/l	0%	1.3%	1	0%	1.2%	1
Q4 (Hcy)	24.1%	24.2%	0.996	20%	24.4%	1
MCV (fL)	89.3±7.3	85.8±7.1	0.074	89.5±8.9	86.2±7.1	0,399
Folic acid (µg/l)	10.5±5.3	9.7±5.2	0.412	12.2±6.3	9.7±5.1	0.196
B12 vitamin (ng/l)	240±183	244±163	0.39	223±153	245±167	0.505

BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, AF: Atrial fibrillation, NIHSS: National Institutes of Health Stroke Scale, tPA: Tissue plasminogen activator, Hcy: Homocysteine, MCV: Mean corpuscular volume, Q4: Homocysteine 4th quarter by level

with cerebral hemorrhage and that hyperhomocysteinemia was not an independent risk factor for hemorrhagic transformation, similar to our study (31,32).

Study Limitations

Our study has some limitations. The study was conducted retrospectively and the presence of correlation could not be excluded due to the small number of patients. Plasma Hcy level can be affected by age, gender, smoking, coffee consumption, protein consumption, drugs (antiepileptics, fibrates, diuretics, etc.), kidney and thyroid functions (33). It was not possible to evaluate all of these factors in patients.

Conclusion

In our study, despite the previously reported effects of increased Hcy levels on antifibrinolytic and vascular integrity, a significant effect of Hcy level on iv tPA efficacy, prognosis and complications was not demonstrated. If there is an effect, it has to be a low-to-moderate effect, and there is a need for prospective studies with large participation in order to reveal such effect.

Ethics

Ethics Committee Approval: Ethical approvals were obtained from the Hacettepe University Non-Invasive Clinical Research Ethics Committee for the stroke database and the project (decision no: 2022/07-48, date: 19.04.2022).

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: E.Y., E.S.G., E.M.A., M.A.T., Concept: E.Y., E.S.G., E.M.A., M.A.T., Design: E.Y., E.S.G., E.M.A., M.A.T., Data Collection or Processing: E.Y., E.S.G., E.M.A., M.A.T., Analysis or Interpretation: E.Y., E.S.G., E.M.A., M.A.T., Literature Search: E.Y., E.S.G., E.M.A., M.A.T., Writing: E.Y., E.S.G., E.M.A., M.A.T.

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