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Original Research

Effect of Air Transport Delay on Mortality in Critical Illness: A Population-Based Cohort Study

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A B S T R A C T

Objective: For critically ill patients in remote areas, we assessed the association of transport delay via fixed wing air ambulance on 30-day mortality, excluding interhospital transports.
Methods: This was a retrospective cohort analysis of all such adult transports in Manitoba, Canada, over 5.4 years. Causal mediation analysis was used, with the Acute Physiology and Chronic Health Evaluation II Acute Physiology Score at the destination intensive care unit as the mediator. The covariates were age, sex, comorbidities, socioeconomic status, and physiologic variables from the sending site.
Results: The primary cohort was composed of 554 patients; 113 (20.4%) died within 30 days. The total transport delay (mean ± standard deviation) was 5.1 ± 1.7 hours. Compared with no delay, the average 5-hour transport delay was associated with an odds ratio for mortality of 1.34 with a 95% confidence interval from 40% lower to 270% higher, with 60% of the influence of total travel time attributable to worsening of patients' acute physiologic status during the delay in intensive care unit admission due to transport.
Conclusions: Although these findings provide insufficient evidence for an effect of fixed wing air transport delay on mortality among critically ill patients, they underscore the need for additional and larger studies on this topic.

Critically ill patients require highly specialized care that is generally provided in specialized locations, such as the intensive care units (ICUs) of acute care hospitals. Most critically ill patients experience some delay before ICU admission, and there has long been concern that delays result in worse outcomes.[1] This concept is best known as the "golden hour" in trauma care.[2] A small amount of evidence suggests that even delays in ICU admission from emergency departments and wards of the same hospital increase mortality.[3,4] This is a complicated issue, subtending different types of critical illness and numerous diagnostic and therapeutic interventions, each combination of which arguably deserves to be evaluated for the nature of its delay-outcomes relationship. For example, in sepsis, the literature is inconsistent regarding the relationship between survival and delayed initial antibiotics[5,6] and resuscitation.[7,8] Indeed, whether 1 hour is a critical threshold is uncertain even in trauma care.[9,10]

The longest treatment delays occur for patients who become critically ill far from the nearest ICU, necessitating critical care air transport. This is not only necessary in large, sparsely populated countries such as Canada and Australia,[11,12] but even in more modestly sized countries with remote areas, such as Norway, Denmark, and Azerbaijan.[13-15] A large and increasing number of regions in the United States lack any ICU beds,[16] requiring such transport.

Air ambulance transport may be by helicopter or fixed wing aircraft. The latter have far longer range, whereas the former can land close to the location of patients, even at the scenes of accidents. Most of the published literature on air transport is restricted to helicopters; a European Union report on emergency transport found so little information about fixed wing transport that it was excluded from consideration.[17] In addition, most of the literature has been focused

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on the transport of trauma patients,[2,15,18-20] who compared with air-transported nontrauma patients generally have lower severity of illness and lower burdens of comorbidity.[14]

There are multiple reasons to be concerned about the effects on the outcomes of air transport of critically ill patients. The travel and transfer time itself, even with the critical care capabilities afforded in many air ambulances, may delay some diagnostic and treatment modalities and lead to deterioration of the patient's physiologic status. Also, intubation and deep sedation are often performed routinely in air transport[21] despite strong evidence that deep sedation, in the admittedly different setting of the ICU, is harmful and usually unnecessary.[22]

This study was performed in the Canadian province of Manitoba. Compared with the large US state of Texas, Manitoba's land area is 82%, and the population density is 14% (population of 1.3 million). The only ICUs in the province are in only 2 population centers, both in the south of the province (ie, Winnipeg with a population of 768,000 and Brandon with a population of 49,000). Most of the province is very sparsely populated and far from those ICUs; in some parts, travel times are substantial even to get to a nursing station or rural hospital lacking an ICU. The straight-line distance is 1,000 km from Winnipeg to the most significant northern population center, Churchill, on the Arctic Ocean. During this study, Manitoba's medical air ambulance transport included a helicopter service (Stars, privately run and primarily used for trauma patients; range = 268 km;) and a fixed wing service (LifeFlight, governmentally run; range 1,000 km). Our analysis only included the fixed wing air ambulance transports; every LifeFlight transport included a nurse and a physician trained in emergency medicine, critical care, or anesthesia.

We evaluated the influence of fixed wing air transport delays in ICU admission on mortality among unselected critically ill outpatients with initial presentations to remote acute care sites (hospital emergency departments or regional nursing stations). We hypothesized that among such patients who were transported to an ICU, longer transport delay is associated with higher risk-adjusted, 30-day mortality. We chose this cohort, excluding interhospital transfers and helicopter transport for 2 reasons. First, it is the least studied of all air ambulance transports.[23] More importantly, if our hypothesis is correct, it has important implications for future research. Specifically, it would mandate further studies seeking ways to ameliorate the elevated rates of death resulting from transport delays and, subsequently, the organization of critical care services.

Methods

This retrospective cohort study used 5 linked, existing databases (Table 1) from the Canadian province of Manitoba derived from the province's universal, government-funded, single-payer health care system and held at the Manitoba Centre for Health Policy.[24] The LifeFlight database included sending and accepting locations and times of initial request for transport from the sending site, aircraft dispatch, departure for sending airport, arrival at sending airport, departure for destination airport, arrival at destination airport, patient arrival at destination hospital, and patient care transferred to personnel at destination hospital. The Winnipeg ICU Database contains detailed clinical data for all ICU admissions, including admission date/time, the total Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and its Acute Physiology Subscore (APS).[25] It identified the time of the initial admission to any of the 11 adult ICUs in the 6 hospitals in the Winnipeg Health Region during the study period.

Table 1
Databases Used for the Study

Name	Content
Patient Registry (A)	Dates of provincial health coverage and date of death
Discharge Abstract Database (A)	Details of all provincial hospitalizations
Medical Claims (A)	Details of all provincial outpatient visits
Winnipeg ICU Database (C)	Clinical data on all admissions to adult intensive care units in the Winnipeg Health Region
LifeFlight (A)	Details of all provincial, fixed wing medical air transports

A = administrative database; C = clinical database.

The following additional data were manually abstracted from photocopied medical records sent with patients from the sending to the receiving sites (Supplemental Appendix 1): facility type (hospital emergency department vs. others), initial triage date/time, the use of life support (as invasive mechanical ventilation and/or continuous infusions of intravenous vasoactive medications), and the worst value before air ambulance arrival of 11 aspects of acute physiologic status (ie, vital signs [heart rate, mean arterial pressure, respiratory rate, and temperature], laboratory values [white blood cell (WBC) count, hemoglobin, sodium, potassium, creatinine, and Pa_{O_2}/fraction of inspired oxygen [F_{IO_2}] ratio), and the Glasgow Coma Scale (GCS) score. The worst values were per APACHE II definitions,[25] except for the Pa_{O_2}/F_{IO2} ratio. For each of these 11 parameters, the worst value in the interval after triage at the sending site and aircraft arrival was chosen and converted to the 0 to 4 ordinal scale per APACHE II definitions,[25] except for the Pa_{O_2}/F_{IO_2} ratio. For that parameter, we used the categories as described by Marshall et al[26]; furthermore, when arterial blood gases had not been performed, we imputed it from the oxygen saturation/F_{IO_2} ratio.[27]

Individuals were included if they were Manitoba residents 18 years or older; transported by fixed wing air ambulance with "emergent" priority between November 1, 2010, and March 31, 2016; and their first inpatient location was a high-intensity, adult ICU in the Winnipeg Health Region. Patients were excluded if they were transported from outside of Manitoba, they were an inpatient in any acute care hospital during the 96 hours before destination arrival (thus excluding interhospital transfers), there was > 6 hours between arrival at the destination hospital and ICU admission, or they were obstetric patients. All eligible subjects were included.

For patients who after ICU admission experienced inter-ICU and/or interhospital transfers, we used the Winnipeg ICU Database and hospitalization data as previously described to reconstruct the entire episodes of posttransport, ICU-containing hospital care,[28] which were the unit of measure for this project. For individuals with multiple such episodes, we only included the first one.

Analysis

Our outcome was mortality at 30 days after admission to the destination hospital ICU. The exposure of interest was the total transport delay (TTD), which was defined as the interval from the initial request for transport from the sending site until admission to the destination hospital ICU. The regression model covariates included age, sex, Charlson Comorbidity Index[29] (calculated using diagnoses listed in the index hospitalization and all inpatient and outpatient claims during the prior 12 months[30] and categorized as 0, 1, or ≥ 2), and socioeconomic status (determined by the SEFI-2 [Socio-economic Factor Index] score with lower status indicated by higher scores).[31]

A key consideration was to appropriately account for the severity of acute illness, 1 of the most influential determinants of short-term mortality in critical illness.[32] In our ICU database, it is assessed as the APACHE II APS, which is calculated from data from the initial ICU day.[25] However, a plausible way that transport delays might cause higher mortality is indirectly via physiologic deterioration during transport. Because simply including APS as a regression model

covariate could obscure the effect of transport delay, we used causal mediation analysis;[33] with APS as the mediator variable it estimates not only the total effect of TTD on the outcome but also partitions it into indirect and direct portions (Supplemental Fig. 1).

Another analytic challenge was created by the possibility that, on average, patients with longer transport delays (generally from more remote areas) would have more severe acute illness. This would confound the relationship between TTD and mortality, biasing it away from the null. For this reason, we included as covariates the following information derived from the sending facility: type (hospital emergency department vs. nursing station), the sending site triage interval (ie, the interval from the initial triage at the sending site until the air ambulance was requested), the use of life support (invasive mechanical ventilation or vasoactive drugs) before air ambulance arrival, and the 11 physiologic measures listed earlier. Using multiple imputation for missing values of sending site WBC count, creatinine, temperature, and GCS, we generated 100 complete data sets (Supplemental Appendices 1 and 2, Supplemental Table 1, Supplemental Figure 2). The 26 variables used in imputation were 1) the actual values for variables from the sending site; 2) age, sex, and socioeconomic status (determined by the SEFI-2 score), and 3) APACHE II–related parameters from the first day in the ICU at the receiving hospital (ie, heart rate, mean arterial pressure, respiratory rate, temperature, WBC count, hemoglobin, sodium, potassium, creatinine, and GCS). After imputation, we converted the missing values to the 0 to 4 ordinal scale as described previously. Following the study by Lall,[34] we evaluated the appropriateness of imputation by assessing whether missingness was strongly related to 1 or a just a few of the observed variables.

A final analytic issue was that our analysis was at risk for model overfitting from including too many independent variables for the number of outcomes.[35] Although the well-known rule of at least 10 events/variable has support,[36] other work indicates that 5 to 9 events/variable may be sufficient.[37] Accordingly, we performed variable reduction on the 11 sending site physiologic variables via principal component analysis[38] using the mean correlation method of van Ginkel et al[39] as recommended for combining it with multiple imputation (Supplemental Appendix 1). The goal was to include as much of the information content of those 11 variables as possible while avoiding model overfitting for the 113 events in our primary analysis. In line with the Kaiser-Guttman rule,[40] we retained the 4 principal components with eigenvalues > 1, which for our 113 outcomes resulted in 14 model covariates, providing 8.1 outcomes/variable. In a sensitivity analysis, we included only the single most influential component, providing 10.3 outcomes/variable.

In a sensitivity analysis, we restricted consideration to the 486 records without any missing covariate data elements. We separately performed principal component analysis on this smaller data set.

Statistical analysis was performed using SAS Version 9.4 (SAS Institute, Cary, NC). The primary interpretation used 95% confidence intervals (CIs).[41]

Results

Over the 65 months of the study, there were 737 unique adults transported by fixed wing air ambulance, 630 of whom met all the inclusion and exclusion criteria; 85 were then excluded for missing physiologic parameters from the sending site other than temperature, WBC count, creatinine, and GCS (Supplemental Appendix 1, Fig. 1). Of the remaining 554 records, 468 had no additional missing parameters, whereas 68 (12.3%) required imputation of 1 or more of sending site temperature, WBC count, creatinine, and GCS. GCS had the most missing cases (32 representing 5.8% of records). The results of the logistic regression model for missingness of any of temperature, WBC count, creatinine, or GCS was highly significant (χ^2 = 41.3, P = .0075), with the dominant predictor being that the patient was sent from a medical site other than the emergency department of a hospital (Supplemental Table 3; odds ratio = 3.3, P = .001).

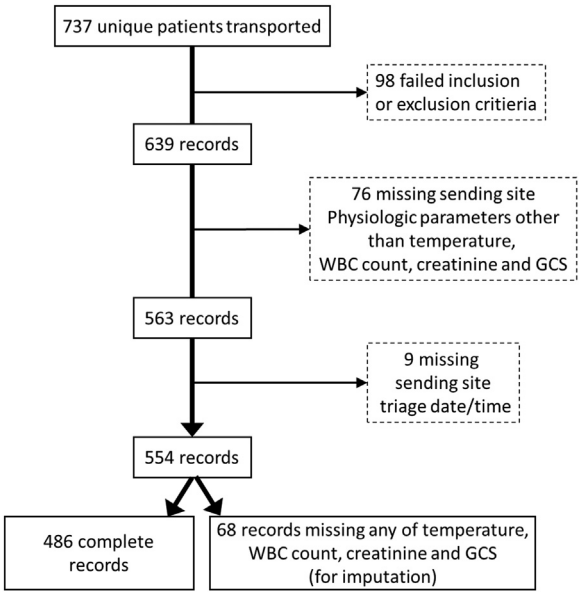

Figure 1. The Consolidated Standards of Reporting Trials diagram.

The baseline characteristics of this cohort (Table 2) showed that most were males transported from hospital emergency departments who received life support at the sending site. The mean time from the initial triage to requesting air transport was 13.2 hours. The mean TTD was 5.1 hours, ranging from 1 to 12 hours. The air travel time and the time on the ground at the sending site averaged 1.7 and 1.9 hours, respectively, each approximately one third of the TTD.

The 4 retained principal components included 57% of the variation (information content) of the original 11 sending site physiologic variables (Supplemental Tables 1 and 2).

Primary analysis on the primary cohort of 554 air-transported patients (Tables 3 and 4, Supplemental Table 4) gave a point estimate indicating higher 30-day mortality with an odds ratio of 1.06 per hour of transport delay (95% CI, 0.89-1.22). On average, 60% of the influence of the total travel time was attributed to worsening of patients' acute physiologic status during the delay in ICU admission due to transport; this is also consistent with a systematically higher APS with a longer total transport time (Table 4). The results were essentially unchanged including only the most influential principal component (Supplemental Table 5). Sensitivity analysis including only the 486 complete records showed similar results (Table 3); the odds ratio for 30-day mortality was 1.05 (95% CI, 0.88-1.24) for the 486 complete records and 1.06 (95% CI, 0.89-1.22) for the 554 records including imputed data.

The relevance of including the severity of illness at the sending site in the analysis is demonstrated by performing analysis without the sending site variables (Table 3). Those results showed a much greater detrimental impact of travel time, with the total effect of the odds of 30-day mortality being 1.31-fold higher for each hour of transport delay (95% CI, 1.12-1.53).

Table 2
Baseline Characteristics and Outcomes of the Final Cohort

Variable	Value	N
Sociodemographic variables		
Age	56.0 ± 16.1	554
Female sex	227 (41.0)	554
Charlson Comorbidity Index		554
0	221 (39.9)	
1	143 (25.8)	
≥ 2	190 (34.3)	
SEFI-2 (Socioeconomic Index)[a]	1.00 ± 1.36	554
Variables from the sending site		
Facility type		554
Hospital emergency department	469 (84.7)	
Regional nursing station	85 (15.3)	
Life support in the sending site[b]	373 (67.3)	554
Sending site triage interval (h)[c]	13.2 ± 18.8	554
Time of day of initial arrival at sending site (24-h day)	12.8 ± 6.2	554
Heart rate (beats/min)	104 ± 42	554
Mean arterial blood pressure (mm Hg)	72.3 ± 30.3	554
Respiratory rate (breaths/min)	27 ± 10	554
Temperature (°C)	36.4 ± 1.7	538
Serum sodium (mmol/L)	138 ± 10	554
Serum potassium (mmol/L)	4.3 ± 1.1	554
Serum creatinine (μmol/L)	199.2 ± 242.6	533
WBC count (1,000/μL)	14.4 ± 8.1	531
Hematocrit (%)	37.2 ± 8.8	554
Pa_{O_2}/F_{IO2} ratio	332 ± 158	554
Glasgow Coma Scale score	8.9 ± 5.6	522
Air transport-related variables		
Straight-line travel distance (km)	454 ± 185	554
Total transport time/delay (h)	5.1 ± 1.7	554
Air travel time (h)	1.7 ± 0.7	554
Time on ground during pickup (h)	1.9 ± 0.9	554
Time from landing at destination airport to ICU admission (h)	1.6 ± 1.7	554
Variables from admitting ICU		
Most responsible hospital diagnosis category		554
Cardiovascular	257 (46.4)	
Infection	82 (14.8)	
Respiratory	62 (11.2)	
Trauma	46 (8.3)	
Neuropsychiatric	42 (7.6)	
Poisoning/overdose	26 (4.7)	
Others	39 (7.0)	
APACHE II Acute Physiology Score	11.1 ± 6.8	554
Total APACHE II score	18.3 ± 9.8	554
Heart rate (beats/min)	90 ± 35	554
Mean arterial blood pressure (mm Hg)	76.1 ± 26.8	554
Respiratory rate (breaths/min)	23 ± 9	554
Temperature (°C)	37.1 ± 1.2	554
Serum sodium (mmol/L)	138.3 ± 6.4	554
Serum potassium (mmol/L)	4.1 ± 1.0	554
Serum creatinine (μmol/L)	170.7 ± 213.2	554
WBC count (1,000/μL)	14.3 ± 8.2	554
Hematocrit (%)	33.9 ± 7.9	554
Glasgow Coma Scale score	10.2 ± 2.4	554
Outcomes		
Hospital length of stay (h)	23.9 ± 42.8	554
30-day mortality	113 (20.4)	554

APACHE II = Acute Physiology and Chronic Health Evaluation II; F_{IO_2} = fraction of inspired oxygen; ICU = intensive care unit.
The values are mean ± standard deviation or n (%).
[a] Population distribution has a mean of 0 and a standard deviation of 1.0; higher values indicate lower status.
[b] Invasive mechanical ventilation and/or continuous infusions of intravenous vasoactive agent(s).
[c] The interval from the initial presentation at the sending site until air transport was requested.

Discussion

We assessed the association of 30-day mortality to delays in transporting unselected critically ill patients from remote areas to ICUs using fixed wing air ambulances. For the average travel delay of 5 hours, the point effect was 33.8% higher odds of death compared with no delay, with a 95% CI ranging from 40% lower to 270% higher; approximately 60% of the point effect is attributable to physiologic deterioration during the travel delay.

Because these findings did not satisfy the usual criteria for statistical significance, our study provides insufficient evidence of an effect of delay on mortality. However, because our study is not inconsistent with a substantial detrimental effect of longer transport times on mortality, it underscores the need for additional and larger studies on this topic. Consistent findings that such air ambulance transports do not lead to worse outcomes would provide reassurance for the care of critically ill patients transported long distances to the nearest ICU. However, if such a transport does worsen outcomes, it would have important implications for the organization of critical care in remote areas. Specifically, it would indicate the need for some combination of: shortening air transport (eg, using a faster aircraft), providing more stabilization and treatment at the sending site, or reducing the need for long transports by establishing ICUs in remote, underserved areas.

The relevance of this topic derives from 1) the increasing need for distant transport to the nearest ICU as indicated earlier and 2) an extreme paucity of prior evidence. Only 1 prior study has assessed the influence of air ambulance transport of critically ill patients not limited to trauma patients and not limited to interhospital transports; the Danish study compared the time to death over 1 year among critically ill patients transported to the hospital via helicopter versus ground ambulance when the helicopter was called but unavailable.[23] Although the reported hazard ratio for helicopter transport was 0.94 (95% C.I. 0.84-1.06), the analysis did not account for actual travel times and included no adjustment for the severity of acute illness. The latter is relevant because among helicopter transports nontrauma patients have a systematically lower severity of illness.[14]

Our study has notable strengths. First, it is a population-based study of all such fixed wing transports in a Canadian province over 5 years. By including all types of ICU admissions rather than being restricted to trauma patients, our results are applicable to a wide range of patient presentations. Second, our study used a rigorous statistical approach that avoids incorrect conclusions by performing causal mediation analysis and including measures of severity of acute illness at both the sending and destination sites. A comparison of the top and bottom halves of Table 3 illustrates that failing to include sending site information greatly overestimates the effect of travel delay on mortality.

Our study also has limitations. Despite including a wide range of covariates in our analysis, residual confounding is always possible, which could be negative confounding.[42] Despite using all available data from an entire province over a number of years, the relatively small number of mortality events (113) could have resulted in a type 2 error. Only considering subjects who reached the ICU alive could have conceivably resulted in survival bias, which for our outcome would be expected to bias toward the null.[43] However, we consider this unlikely because during our study interval the LifeFlight database contained only 10 patients who died after the initial request for transport from the sending site but before they could be admitted to the destination ICU. Finally, the results from a single Canadian province might not be applicable to other jurisdictions. In particular, with substantial variation in the aircraft personnel transporting

Table 3
Primary Mediation Analysis Results: The Effect of Each 1 Hour of Total Travel Time on 30-Day Mortality

	N = 554, Including Imputed Data (113 With the Outcome)		N = 486, Complete Records Only (91 With the Outcome)	
	Odds Ratio	95% CI	Odds Ratio	95% CI
Including sending site covariates				
Total effect	1.06	0.89-1.22	1.05	0.88-1.24
Direct effect	1.02	0.87-1.18	1.02	0.85-1.19
Indirect effect	1.03	0.99-1.07	1.03	1.00-1.08
Percentage mediated	59.8		67.2	
Excluding sending site covariates				
Total effect	1.31[a]	1.12-1.53	1.26[a]	1.08-1.46
Direct effect	1.13	0.97-1.32	1.11	0.96-1.30
Indirect effect	1.16[a]	1.10-1.24	1.14[a]	1.07-1.21
Percentage mediated	58.8		57.2	

CI = confidence interval.
[a] The CI did not include the null result.

Table 4
Ordinary Least Squares Regression Model of the Mediator Variable (Acute Physiology and Chronic Health Evaluation II Acute Physiology Score) at the Destination Site Intensive Care Unit (N = 554)

Parameter	Including Sending Site Data			Excluding Sending Site Data		
	Coefficient	95% CI	*P* Value	Coefficient	95% CI	*P* Value
Age (per year)	0.006	−0.021 to 0.033	.66	−0.029	−0.063 to 0.006	.11
Female sex (compared with male)	0.543	−0.293 to 1.378	.20	1.165	0.101-2.229	.03
Charlson Comorbidity Index						
0	Reference			Reference		
1	0.809	−0.207 to 1.825	.12	1.927	0.618-3.237	.0039
≥ 2	1.550	0.542-2.561	.003	4.391	3.145-5.636	<.0001
SEFI-2 (Socioeconomic Index)[a]	0.196	−0.166 to 0.558	.29	0.687	0.267-1.107	.0014
Sending site type						
Hospital emergency department	Reference					
Regional nursing station	0.145	−1.114 to 1.405	.82			
Life support at sending facility[b]	1.706	0.505-2.907	.005			
Sending site triage interval[c] (per hour)	0.001	−0.021 to 0.023	.92			
Principal component 1[d]	1.926	1.687-2.166	< .0001			
Principal component 2[d]	−1.053	−1.290 to −0.816	< .0001			
Principal component 3[d]	0.058	−0.212 to 0.328	.67			
Principal component 4[d]	−0.330	−0.709 to 0.049	.088			
Total transport time (per hour)	0.266	0.012-0.520	.04	0.972	0.664-1.280	< .0001

CI = confidence interval.
[a] Population distribution has a mean of 0 and standard deviation of 1.0; higher values indicate a lower status.
[b] Invasive mechanical ventilation and/or continuous infusions of intravenous vasoactive agent(s).
[c] The interval from the initial presentation at the sending site until air transport was requested.
[d] Derived from 11 variables per Supplemental Appendix 1.

patients,[11] it is possible that the Manitoba practice of including a physician and nurse could have resulted in lower mortality compared with other staffing paradigms.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amj.2022.09.001.

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