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Original Article

Real-world cost-effectiveness of targeted temperature management in out-of-hospital cardiac arrest survivors: results from an academic medical center

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BACKGROUND: Targeted temperature management (TTM) is a common therapeutic intervention, yet its cost-effectiveness remains uncertain. This study aimed to evaluate the real-world cost-effectiveness of TTM compared with that of conventional care in adult out-of-hospital cardiac arrest (OHCA) survivors using clinical patient-level data.

METHODS: We conducted a retrospective cohort study at an academic medical center in the USA to assess the cost-effectiveness of TTM in adult non-traumatic OHCA survivors between 1 January, 2019 and 30 June, 2023. The primary outcome was survival to hospital discharge. Incremental cost-effectiveness ratios (ICERs) were calculated and compared with various decision makers' willingness to pay. Cost-effectiveness acceptability curves were utilized to evaluate the economic attractiveness of TTM. Uncertainty about the incremental cost and effect was explored with a 95% confidence ellipse.

RESULTS: Among 925 non-traumatic OHCA survivors, only 30 (3%) received TTM. After adjusting for potential confounders, the TTM group did not demonstrate a significantly lower cost (delta cost -$5,141, 95% confidence interval [95% *CI*]: $-35,347 to $25,065, *P*=0.79) and higher survival to hospital discharge (delta effect 6%, 95% *CI*: -11% to 23%, *P*=0.41). Additionally, a 95% confidence ellipse indicated uncertainty reflected by evidence that the true value of the ICER could be in any of the quadrants of the cost-effectiveness plane.

CONCLUSION: Although TTM did not demonstrate a clear survival benefit in this study, its potential cost-effectiveness warrants further investigation with larger sample sizes. These findings highlight the need for additional research to optimize TTM use in OHCA care and inform resource allocation decisions.

KEYWORDS: Out-of-hospital cardiac arrest; Targeted temperature management; Cost-effectiveness; Survival; Real-world data

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INTRODUCTION

Sudden cardiac arrest poses a significant critical medical challenge and is the third leading cause of death worldwide.[1] The global survival rate for out-of-hospital cardiac arrest (OHCA) patients is approximately less than 10%.[2] In the USA, OHCA affects 400,000 people annually,[3] with approximately one quarter hospitalized for post-resuscitation therapy.[4] Additionally, successful resuscitation often results in severe neurological injury, with irreversible brain damage being the most common cause of death in the post-cardiac arrest phase.[5]

Traditionally, cardiac arrest survivors have had limited treatment options, which mainly rely on supportive care.[6] As documented in previous

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studies, targeted temperature management (TTM) post-cardiac arrest has shown promising results in improving neurological and survival outcomes.[7,8] Current guidelines by the American Heart Association recommend that TTM be provided in all comatose OHCA patients with the return of spontaneous circulation (ROSC).[9] However, TTM has not been fully implemented across USA hospitals.[10] Previous studies reported that only one-third of potential candidates received TTM. Additionally, the TTM utilization rates in the USA decreased from 58% to 27% between 2012 and 2015. The implementation of TTM as a standard of care for post-cardiac arrest patients faces several challenges, with cost being a significant factor.[11] TTM involves the use of specialized devices and careful monitoring to induce and maintain a specific target temperature.[12] These devices, along with the required monitoring equipment and personnel training, contribute to the additional expense of TTM implementation.

Previous studies exploring the cost-effectiveness of TTM reported cost savings with various types of TTM being assessed, such as cooling blankets, cooling caps, and intravascular cooling devices.[6,13,14] However, these studies were limited in that they did not employ patient-level data. The incorporation of real-world cost-effectiveness data into a cost-effectiveness analysis (CEA) can offer insights into the economic viability and implementation challenges of TTM in healthcare settings. We aimed to evaluate the real-world cost-effectiveness and implementation of TTM compared with those of conventional supportive care following OHCA in an academic university hospital. Our results will inform evidence-based decision-making in policy and practice, offering practical implications for healthcare stakeholders and policymakers aiming to optimize post-cardiac arrest care protocols and resource allocation strategies.

METHODS

Study design and study population

We conducted a CEA to assess the effectiveness of TTM for comatose adult patients (≥18 years) who survived OHCA presenting at the emergency department (ED) of the University of California Davis Medical Center (UCDMC) between 1 January, 2019 and 30 June, 2023 from a hospital perspective. UCDMC is an academic tertiary hospital serving 65,000 square miles of area, including 33 counties and 6 million residents across Northern and Central California. Following standard guidelines during the study period, we provided TTM for all comatose OHCA survivors if there were no contraindications. The specific TTM protocol involved inducing hypothermia within 6 h of ROSC to a target temperature of 34 °C, maintaining this temperature for 24 h, and then gradually rewarming over 24 h. The exclusion criteria were those with presumed traumatic cardiac arrest (i.e., witnessed reporting a direct cause of cardiac arrest related to falls, accidents, or assault, evidence of external trauma such as visible injuries or bleeding) and those who died in the ED (i.e., did not survive until admission).

Ethical considerations

We obtained ethical approval from the Institutional Review Board of the University of California Davis School of Medicine. Informed consent was waived because of the anonymous and retrospective nature of the data. We reported findings following the Strengthening the Reporting of Observational Studies in Epidemiology[15] and the Consolidated Health Economic Evaluation Reporting Standards 2022 statements.[16]

Data collection and study variables

We retrospectively collected the following information through the hospital's electronic medical records search for those who presented between January 2019 and June 2023, including patient age at cardiac arrest, sex (male/female), race (White/African American/Asian/others), ethnicity (Hispanic/non-Hispanic), day of the event (weekday/weekend), comorbidities (diabetes, malignancy, hypertension, chronic kidney disease, hyperlipidemia, stroke, chronic pulmonary disease, myocardial infarction, chronic heart failure, peripheral vascular disease, dementia, chronic liver disease), co-interventions (extracorporeal cardiopulmonary resuscitation, percutaneous coronary intervention), hospital length of stay, and total costs. The Charlson Comorbidity Index was also calculated to assess the burden of comorbidities in the study population. Cardiac arrest patients were identified via the International Classification of Diseases, tenth revision (ICD-10) codes. The following ICD-10 codes were used to capture cases of cardiac arrest: I46 (cardiac arrest), I46.0 (sudden cardiac arrest), I46.2 (cardiac arrest due to underlying cardiac condition), I46.8 (cardiac arrest due to other underlying conditions), and I46.9 (cardiac arrest, cause unspecified).

Variables

Clinical outcomes

The effect (outcome of interest) was survival to hospital discharge status (yes/no), defined as either being discharged from the hospital regardless of their neurological status or being discharged against medical advice (leaving the hospital without the permission of their treating physicians).

Cost

The costs were obtained from hospital billing records. Total costs were the sum of direct and administrative costs over the patient's hospital length of stay. Direct costs covered services to patients in the ED and the inpatient department. Administrative costs include costs to support overall patient services in non-patient care.

Evaluation of cost-effectiveness

Using a net benefit regression framework, we compared the total cost and survival to hospital discharge status for both study groups (TTM and no TTM). The extra cost (ΔC, the difference in total costs between the TTM and non-TTM groups), extra effect (ΔE, the difference in survival to hospital discharge between the TTM and non-TTM groups), incremental cost-effectiveness ratio (ICER, ΔC/ΔE), and incremental net benefit (INB) were estimated. Theoretically, a TTM is cost-effective if a more effective treatment has an ICER less than the decision maker's willingness to pay (WTP) for it. In this study, ΔC and ΔE were calculated from different regression models adjusted for confounders.

The INB is commonly used to evaluate the cost-effectiveness of interventions in economic evaluations.[17] It is calculated by considering costs, outcomes, and net benefit differences between patients with TTM and those without TTM. We obtained the INB by multiplying the extra effect by a WTP threshold and subtracting the extra cost (WTP × ΔE - ΔC). A positive INB indicates the cost-effectiveness of TTM in OHCA survivors, whereas a negative INB suggests otherwise. We also presented the cost-effectiveness acceptability curve (CEAC) to illustrate the probability that TTM is cost-effective.[18]

Statistical analysis

Categorical variables are presented as frequencies and proportions and were compared via the Chi-square test (or Fisher's exact test for counts less than 5 with a 2×2 table). For continuous variables, the means±standard deviations or medians with interquartile ranges were used as appropriate. The independent *t*-test was used for comparison. A *P*-value of less than 0.05 was considered statistically significant. All analyses used STATA MP, version 16 (StataCorp, USA).

RESULTS

Patient characteristics

In total, 2,424 adult OHCA records were identified. Among these patients, 1,086 were presumed to have experienced traumatic cardiac arrest, and 413 died in the ED. Thus, a total of 925 patients were included in the analysis, with 30 (3%) patients in the TTM group and 895 (97%) in the non-TTM group (Figure 1). In contrast to the non-TTM group, the TTM group had fewer White, African American, and Asian individuals (35% vs. 45%, 7% vs. 17%, and 4% vs. 12%, respectively, *P*=0.01) and more Hispanic individuals (35% vs. 17%, *P*=0.02). Additionally, patients in the TTM group had a lower medical history of malignancy than did those in the non-TTM group (3% vs. 17%, *P*=0.05). In addition, the Charlson Comorbidity Index of patients in the TTM group was lower than that of patients in the non-TTM group (3.7 vs. 5.3, *P*=0.007). Table 1 shows the baseline characteristics and demographics of the included participants.

Clinical outcomes

TTM was not associated with significantly improved survival to hospital discharge either when unadjusted (crude odds ratio [*OR*] 1.21, 95% confidence interval [95% *CI*]: 0.58–2.54, *P*=0.62) or adjusted for potential confounding factors (adjusted *OR* 1.31, 95% *CI*: 0.60–2.90, *P*=0.50).

Cost-effectiveness analysis

For patients with TTM, the median direct and

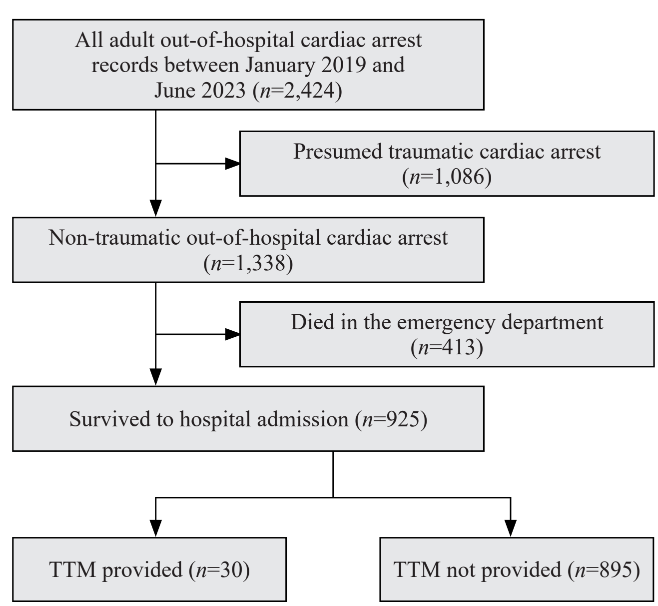

Figure 1. Study flow chart. TTM: targeted temperature management.

administrative costs were not significantly higher than those without TTM ($45,320 vs. $37,529, *P*=0.25 and $27,690 vs. $23,969, *P*=0.30, respectively). We also explored means, as CEA is performed by comparing differences in means. Compared with conventional care (no TTM), unadjusted mean costs were $-35,768 (95% *CI*: $-98,013 to $26,476) lower, and unadjusted mean survival to hospital discharge was 4% (95% *CI*: -13% to 22%) higher in the TTM group. Similarly, adjusted mean costs were $-5,141 (95% *CI*: $-35,347 to $25,065) lower, and adjusted mean survival to hospital discharge was 6% (95% *CI*: -11% to 23%) higher in the TTM group. The adjusted ICERs were negative because of the estimates of cost savings and additional survival to hospital discharge (supplementary Table 1).

On the basis of list prices, the CEAC illustrates that the probability of TTM being cost-effective was 63%, 67%, and 73% if the WTP threshold was $50,000, $100,000, and $250,000/additional survival to hospital discharge, respectively (supplementary Figure 1). Our findings have important uncertainty with respect to the CEAC and the 95% *CI*s of the INB results, which include zero (Figures 2 and 3).

DISCUSSION

We evaluated the cost-effectiveness of TTM in patients who survived from non-traumatic OHCA to improve survival to hospital discharge. Our findings revealed that TTM was not significantly associated with increased survival to hospital discharge. The average total costs for patients with TTM were similar to those without TTM.

TTM is a class I recommendation for comatose

Table 1. Characteristics and demographics of the included participants

Variables	Total (*n*=925)	TTM (*n*=30)	Non-TTM (*n*=895)	*P*-value
Age, years, mean±SD	61.4±16.3	59.6±12.6	61.4±16.4	0.54[a]
Age categories, *n* (%)				0.46[b]
18–49 years	200 (22)	8 (27)	192 (22)	
50–69 years	420 (45)	15 (50)	405 (45)	
≥70 years	305 (33)	7 (23)	298 (33)	
Male, *n* (%)	573 (62)	17 (57)	556 (62)	0.55[b]
Race, *n* (%)				0.01[c]
White	398 (44)	10 (35)	388 (45)	
African American	147 (16)	2 (7)	145 (17)	
Asian	103 (12)	1 (4)	102 (12)	
Native Hawaii/Pacific islanders	19 (2)	3 (10)	16 (2)	
American Indian/Alaskan Native	4 (1)	0 (0)	4 (1)	
Others/Preferred not to state	226 (25)	13 (45)	213 (25)	
Ethnicity, *n* (%)				0.02[b]
Hispanic	156 (17)	10 (35)	146 (17)	
Non-Hispanic	758 (83)	19 (66)	739 (84)	
Day of the event, *n* (%)				0.29[b]
Weekday	695 (75)	20 (67)	675 (75)	
Weekend	230 (25)	10 (33)	220 (25)	
Comorbidities, *n* (%)				
Diabetes	269 (29)	5 (17)	264 (30)	0.15[c]
Malignancy	155 (17)	1 (3)	154 (17)	0.05[c]
Hypertension	197 (21)	9 (30)	188 (21)	0.24[b]
Chronic kidney disease	284 (31)	7 (23)	277 (31)	0.37[b]
Hyperlipidemia	255 (28)	5 (17)	250 (28)	0.22[c]
Stroke	92 (10)	4 (13)	88 (10)	0.53[c]
Chronic pulmonary disease	215 (23)	8 (27)	207 (23)	0.65[b]
Myocardial infarction	338 (37)	11 (37)	327 (37)	0.99[b]
Chronic heart failure	411 (44)	13 (43)	398 (44)	0.90[b]
Peripheral vascular disease	57 (6)	1 (3)	56 (6)	1.00[c]
Dementia	64 (7)	1 (3)	63 (7)	0.72[c]
Chronic liver disease	121 (13)	2 (7)	119 (13)	0.41[c]
Charlson Comorbidity Index, mean±SD	5.3±3.2	3.7±2.1	5.3±3.2	0.007[a]
Co-interventions, *n* (%)				
Extracorporeal cardiopulmonary resuscitation	8 (1)	0 (0)	8 (1)	1.00[c]
Percutaneous coronary intervention	53 (6)	2 (7)	51 (6)	0.69[c]
Hospital length of stay, d, median (IQR)	7 (2–16)	7 (4–14)	7 (2–16)	0.21[d]
Total costs, $, median (IQR)	61,556 (30,052–134,985)	70,921 (50,580–114,166)	61,080 (29,552–136,790)	0.26[d]
Direct costs, $, median (IQR)	38,253 (18,849–84,633)	45,320 (29,849–73,679)	37,529 (18,414–85,842)	0.25[d]
Administrative costs, $, median (IQR)	24,086 (10,984–52,507)	27,690 (20,731–45,975)	23,969 (10,876–53,306)	0.30[d]

[a]: data were compared via an independent *t* test; [b]: data were compared via the Chi-square test; [c]: data were compared via Fisher's exact test; [d]: data were compared via Wilcoxon's rank sum test. The percentages have been rounded and may not equal 100. TTM: targeted temperature management; IQR: interquartile range; SD: standard deviation.

survivors of OHCA regardless of initial presenting rhythm according to the current AHA guidelines.[9] Despite these recommendations, a previous study revealed that only a quarter of eligible patients received TTM, with significant differences in treatment rates among different levels of hospitals.[10] Although more than three-fourths of OHCA survivors are in a coma,[19] and TTM has been advised in recent decades,[9,19] several obstacles may still prevent it from being routinely used.[20,21] The most common reports included a lack of familiarity with and availability of concrete hypothermia protocols, the high workload of emergency nurses, the availability of equipment, and equipment costs.[20,21] Overall, cost is supposed to be a substantial contributor.[14] Matilla-García et al[22] reported that the median total cost per cardiac arrest was $83,939 (€73,505 in 2020), which is comparable to the findings in our study, i.e., $61,556. Interestingly, previous reports revealed that the total cost increased as the neurological outcome became poorer,[22,23] suggesting the appropriateness and value of investing in TTM for these patients.

It is imperative to address the additional costs associated with TTM[11] (i.e., equipment, devices, laboratories, monitoring process), the few who ultimately survive, and even those who eventually survive with intact neurological function. It could be argued that those with lower expected survival may receive less TTM; however, a recent study reported poor agreement between TTM treatment and mortality.[24] In that study, they suggested an inappropriate use of TTM in patients with higher mortality risk, even though these patients were found to have the longest resuscitation time and would have been expected to have the greatest potential benefit with TTM,[24] highlighting the question of how to optimally deliver and enhance the uptake of guideline recommendations for TTM in OHCA patients. In this case, CEA can help determine whether the costs are justified by benefits associated with its use. Unlike previously published articles that used economic models,[6,13,14] our study employed real-world data from clinical practice in the era when TTM was strongly recommended. We did not find statistically significant incremental costs or incremental patient outcomes (i.e., survival to hospital discharge) of TTM in OHCA survivors. TTM was found to be an independent factor associated with an increase in total costs.[25,26] Our findings are congruent with a recently published study by Dankiewicz et al[7] that revealed that TTM did not result

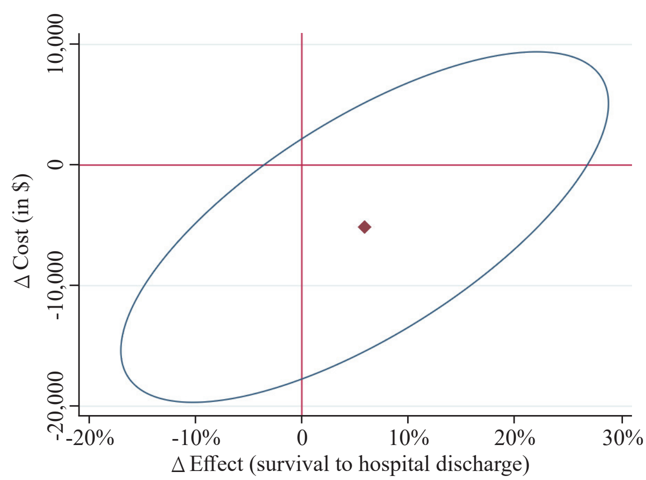

Figure 3. Uncertainty about the incremental cost and incremental effectiveness illustrated on the cost-effectiveness plane with a 95% confidence ellipse.

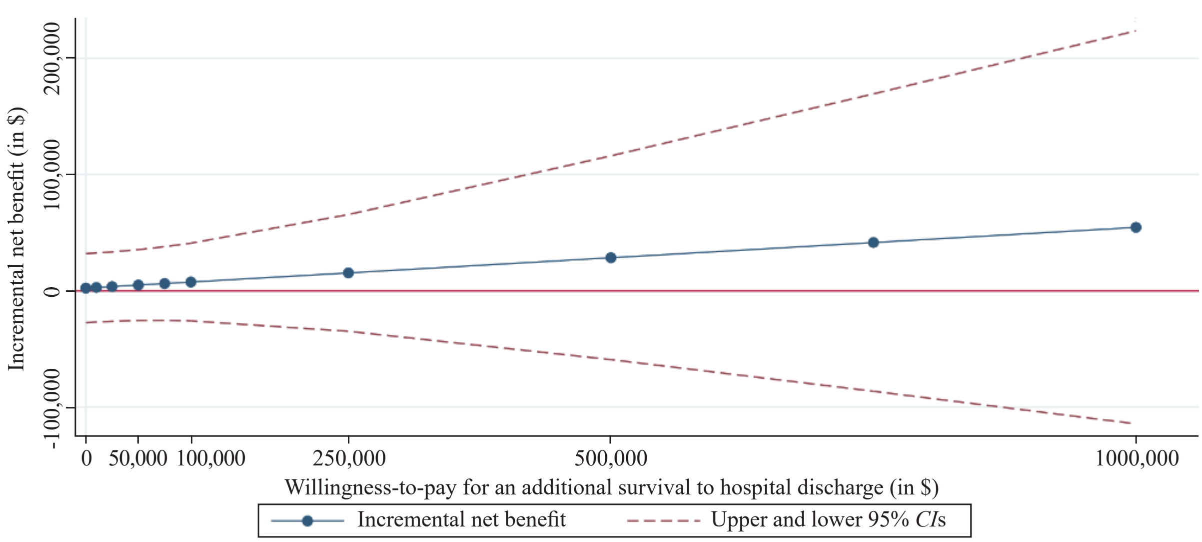

Figure 2. The incremental net benefit by willingness-to-pay plot demonstrates incremental net benefits and their 95% *CI*s for different willingness-to-pay values. 95% *CI*s: 95% confidence intervals.

in lower mortality than normothermia did.

With respect to the implications of our findings from a public health perspective, it is crucial to consider the broader context of resource allocation and healthcare policy. While TTM may benefit these patients, its cost-effectiveness and impact on patient outcomes remain uncertain. Future research should focus on identifying strategies to optimize TTM delivery, addressing barriers to implementation, and assessing its long-term impact on healthcare costs.

Our study has several limitations that need to be addressed. First, this study was conducted at a single academic tertiary hospital, which may limit the generalizability of the findings to other healthcare settings with different populations, resource allocations, and clinical practices. Second, the relatively small number of patients receiving intervention (3%) may have limited the statistical power to detect significant differences in outcomes between the TTM and non-TTM groups. This small sample size could also lead to lower precision in cost-effectiveness estimates[27] and may not fully represent the broader population of OHCA survivors. Furthermore, as with any retrospective study relying on electronic medical records, there may be some missing potential confounders and inconsistencies or inaccuracies in the documentation of patient information, comorbidities, and healthcare utilization, which could introduce bias or affect the validity of the results. In addition, cost data were obtained from hospital records and may not capture all relevant costs associated with TTM, such as long-term care, rehabilitation, and indirect costs to patients and caregivers; variations in cost estimation methods across different healthcare systems may affect the comparability of cost-effectiveness estimates. Finally, this study primarily focused on survival to hospital discharge as the primary outcome measure, without a detailed assessment of neurological function or quality of life outcomes among survivors. This limits the evaluation of the broader impact of TTM on neurological function and quality of life. Future research should consider incorporating these outcomes to provide a more comprehensive assessment of TTM effectiveness.

CONCLUSION

In conclusion, our study provides valuable insights into the real-world cost-effectiveness of TTM in adult non-traumatic OHCA survivors. While our analysis suggests that TTM may offer good value for money when costs and effects are considered together, the small sample size and the lack of a statistically significant improvement in survival to hospital discharge highlight the uncertainty of these findings. These results underscore the importance of jointly considering cost and effect in decision-making regarding TTM implementation in post-cardiac arrest care. Further research is needed to address this uncertainty and optimize resource allocation strategies in post-cardiac arrest care.

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Ethical approval: The Institutional Review Board (IRB) of the University of California Davis School of Medicine approved this study (Approval No. 2016726-1).
Conflicts of interests: None declared. The abstract was selected for oral presentation at the European Emergency Medicine Congress, 13-16 October 2024, Copenhagen, Denmark.
Contributors: WW, DKN, WI, and JSH conceived the study design and coordinated the study. WW and DKN participated in IRB proposal submittal and data collection. WW verified the data and performed the data cleansing. WW and JSH performed statistical analysis and table and figure design. DKN, WI, and JSH supervised the study process. WW drafted the initial manuscript. DKN and JSH critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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