

Cost-Effectiveness of Sodium Hyaluronate versus Carboxymethylcellulose in Patients with Dry Eye Disease Following Cataract Surgery

Article History:

Accepted: 29 August 2026

Revised: 12 October 2026

Published: 21 October 2026

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Keywords:

Cost effectiveness;

Dry Eye Syndrome;

ICER.

Dry eye disease is a common complication after cataract surgery and often requires artificial tear therapy to alleviate symptoms and improve tear film function. This study aimed to analyse the cost-effectiveness of sodium hyaluronate and carboxymethylcellulose in patients with dry eye following cataract surgery. This study provides clinical and economic evidence to support the selection of effective and efficient artificial tear therapy. A prospective cohort analytical observational design with a Cost-Effectiveness Analysis (CEA) approach was conducted from the healthcare provider perspective. The observation period was 14 days. A total of 151 patients met the inclusion criteria, comprising 71 patients receiving sodium hyaluronate and 80 receiving carboxymethylcellulose. Cost-effectiveness was evaluated using the average cost-effectiveness ratio (ACER), incremental cost-effectiveness ratio (ICER), and one-way sensitivity analysis, with the Schirmer test as the main effectiveness parameter. Sodium hyaluronate demonstrated greater effectiveness than carboxymethylcellulose, with a reduction of 6.7 points in DEQ-5 score, a symptom-free duration of 10.23 days, and an increase of 3.0 mm in Schirmer test values. Based on the Schirmer test, the ACER was IDR 119,305 for carboxymethylcellulose and IDR 128,900 for sodium hyaluronate. The ICER showed that sodium hyaluronate required an additional cost of IDR 176,870 to obtain one additional 1 mm improvement in Schirmer test value compared with carboxymethylcellulose. One-way sensitivity analysis showed that changes in effectiveness had a greater influence on the ICER than changes in cost. Sodium hyaluronate therefore provided greater effectiveness but required higher costs than carboxymethylcellulose.



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Dry eye disease (DED) is an ocular-surface disorder that can compromise comfort and visual function after cataract surgery. Surgical disruption of corneal nerves, ocular-surface inflammation, and

exposure to perioperative topical medications may disturb tear-film homeostasis. The TFOS DEWS II framework identifies loss of tear-film homeostasis, inflammation, and neurosensory abnormalities as

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central features of this multifactorial condition [1]. In a systematic review and meta-analysis, Miura et al. reported that 37.4% of patients without pre-existing DED developed DED following cataract surgery (95% confidence interval, 22.6–52.3%) [1]. The variation between studies also indicates that postoperative DED depends on patient characteristics, diagnostic criteria, and assessment timing. These findings support evaluating treatments that relieve postoperative symptoms while making appropriate use of healthcare resources. Krance et al. also documented additional postoperative healthcare use associated with dry-eye symptoms, supporting the importance of considering service utilization alongside clinical outcomes [3].

Sodium hyaluronate (SH) and carboxymethylcellulose (CMC) are artificial-tear agents used to treat DED. The Korean dry-eye guidelines include artificial tears among the treatment options, with management tailored to the underlying disease subtype and clinical findings [4]. Direct comparative clinical evidence does not establish consistent superiority of either agent. Lee et al. conducted a prospective, randomized, blinded study comparing preservative-free 0.1% SH with 0.5% CMC over eight weeks. Both groups improved in ocular-surface staining, tear-film breakup time, and symptom scores, with no statistically significant between-group differences in the assessed indices [5]. In an observational study of mild-to-moderate DED, Salim et al. likewise reported improvements in symptoms, tear-film breakup time, and Schirmer test results at eight weeks in both treatment groups and concluded that the agents had comparable efficacy [6]. These studies inform the clinical comparison in general DED, but do not establish the incremental economic value of SH over CMC in postoperative patients. A review by Hynnekleiv et al. similarly found that comparative responses to hyaluronic acid and other single-ingredient eye drops varied across formulations and outcome measures [7].

Evidence specific to cataract surgery must also be distinguished by the formulation and

comparator evaluated. In a multicentre study of 282 patients, Mencucci et al. compared a combined 0.1% SH–0.5% CMC formulation added to postoperative steroid–antibiotic treatment with steroid–antibiotic treatment alone. At five weeks, the combination improved tear-film breakup time and visual-analogue symptom scores, whereas Ocular Surface Disease Index scores did not differ significantly between groups [8]. This supports a postoperative role for the combined lubricant, but does not constitute a comparison of SH monotherapy with CMC monotherapy. More recently, Song et al. reviewed 47 randomized trials of topical regimens after cataract surgery; 38 trials contributed to network meta-analyses. No regimen showed consistently favourable effects across all ocular-surface outcomes, and interpretation was limited by sparse direct comparisons and risk of bias [9]. Thus, improvements in individual clinical endpoints cannot by themselves establish which treatment provides better economic value.

Sun et al. compared hydroxypropyl guar/hyaluronic acid with CMC/hyaluronic acid after cataract surgery and found comparable effects on several symptom and tear-function measures at weeks 1 and 3 [10]. Because both formulations contained hyaluronic acid, these results should not be interpreted as a direct comparison of SH and CMC monotherapy. In another postoperative study, Yusufoğlu and Keser reported improvements in tear-film breakup time and Schirmer values at one month when 0.15% SH was added to routine postoperative treatment [11]. These studies support evaluating postoperative ocular-surface outcomes, but neither determines the incremental cost-effectiveness of the two monotherapies examined here.

Economic evidence addresses a separate question: how much additional cost accompanies an additional health benefit? Włodarczyk and Fairchild developed a United States economic model comparing Systane with Refresh Tears and reported a favourable incremental cost per quality-adjusted life-year for Systane under the model assumptions [12].

This study demonstrates that economic comparisons of ocular lubricants already exist. However, its alternatives and decision context differ from a direct comparison of SH and CMC for DED following cataract surgery. Its findings therefore do not resolve whether the additional direct medical expenditure associated with SH is proportionate to its observed postoperative benefits in the present setting.

The specific knowledge gap is the joint estimation of incremental direct medical costs and incremental clinical outcomes for SH versus CMC in patients with post-cataract surgery DED. The clinical studies described above report ocular-surface outcomes without establishing this economic comparison, while the economic model evaluates different treatment alternatives [5,6,8,9,12]. Cost-effectiveness analysis can address this gap by relating the difference in costs to the difference in effectiveness between the two treatments [13]. CHEERS 2022 provides reporting guidance for making the alternatives, analytical perspective, time horizon, costs, outcomes, and uncertainty explicit; it is not evidence that either treatment is cost-effective [14].

The present study links provider-level direct medical costs with three separately reported outcomes: symptom-free days, reduction in Dry Eye Questionnaire-5 (DEQ-5) scores, and improvement in Schirmer test values. DEQ-5 is a validated measure that discriminates between levels of self-reported dry-eye severity [15]. Symptom-free days describe the duration of symptom relief within the observation period, whereas Schirmer test changes provide a complementary measure of tear secretion. Reporting a separate incremental cost-effectiveness ratio (ICER) for each outcome allows the additional expenditure to be interpreted in its corresponding clinical unit without treating these outcomes as interchangeable.

The study's contribution is a direct, outcome-specific economic comparison of SH and CMC in postoperative DED, connecting the clinical comparison with the resource implications of treatment selection. The clinical setting determines the applicability of the estimates, and the 14-day

horizon defines an assessment of early treatment outcomes. Neither feature alone establishes novelty, and the analysis does not establish long-term cost-effectiveness. An ICER expressed per symptom-free day, DEQ-5 point, or Schirmer millimetre also requires an appropriate decision threshold before the additional benefit can be judged economically acceptable [13].

Accordingly, this study aimed to compare the direct medical costs and clinical effectiveness of SH and CMC from the eye-clinic provider perspective over 14 days in patients with DED following cataract surgery. It estimated the additional cost per additional symptom-free day, per additional one-point reduction in DEQ-5 score, and per additional one-millimetre improvement in the Schirmer test, and examined the sensitivity of the estimates to changes in cost and effectiveness inputs.

Results and Discussion

Subject Characteristics

Cost-effectiveness analysis is conducted from the perspective of the service provider, namely the eye clinic. The observation was conducted according to the established time horizon, which is 14 days. The sample obtained consisted of 151 patients with post-operative dry eye syndrome after cataract surgery. As many as 71 patients received sodium hyaluronate therapy, and 80 patients received carboxymethylcellulose therapy.

Direct medical cost and effectiveness

Table 1 shows the average total direct medical costs for sodium hyaluronate therapy amounting to IDR 386,698±11,048, which is higher compared to carboxymethylcellulose therapy amounting to IDR 298,263±14,699. The results of the independent t-test showed a statistically significant difference between the two groups ($p=0.001<0.05$), indicating that the use of sodium hyaluronate requires higher direct medical costs compared to carboxymethylcellulose.

The effectiveness of the therapy is assessed based on three parameters, namely symptom-free days, changes in DEQ-5 scores, and changes in Schirmer test values. The average number of symptom-free days in the SH therapy group was 10.23 days, while in the CMC therapy group it was 8.01 days, resulting in an additional 2.22 days in the SH therapy group. The results of the independent t-test showed a p-value of 0.001 ($p < 0.05$), indicating a statistically significant difference between the two groups.

This indicates that sodium hyaluronate therapy provides a longer symptom-free period compared to carboxymethylcellulose in patients with dry eye after cataract surgery. In this study, symptom-free days represent the duration of reported symptom relief during the 14-day observation period. Expressing cost-effectiveness in natural clinical units allows the incremental cost to be interpreted in

relation to the measured benefit [13]. This outcome should not be treated as a direct measurement of health-related quality of life. On the DEQ-5 parameter, the average score decreased by 6.7 ± 2.6 points in the SH therapy group and 5.5 ± 2.1 points in the CMC therapy group. The difference in DEQ-5 score changes between the two groups showed statistically significant results ($p = 0.003 < 0.05$). These results indicate a greater observed reduction in subjective dry-eye symptoms with SH during this study period. However, Salim et al. reported comparable efficacy of SH and CMC at eight weeks [6]. The meta-analysis by Savitri and Hanif reported advantages for SH in tear-film breakup time and corneal staining, but no statistically significant difference in subjective symptom scores [16]. Therefore, the present symptom findings should be interpreted in the context of the postoperative population, outcome instrument, and shorter observation period.

Table 1. Comparison of Average Direct Medical Costs and Therapy Effectiveness

Parameter	Sodium Hyaluronate	Carboxymethylcellulose	Difference	P-Value*
Direct medical costs (IDR)	386.698	298.263	88.435	0,001
Symptom-free days (days)	10,23	8,01	2,22	0,001
DEQ-5 score (points)	6,7	5,5	1,2	0,003
Schirmer test (mm)	3,0	2,5	0,5	0,001

*independent t-test

In this study, a cost analysis was conducted from the perspective of the service provider, namely the clinic. Based on the research results, the components and the amount of cost for each patient during treatment were obtained. Based on the collected data, the components of direct medical costs consist of administrative and doctor fees, slit lamp examination fees, artificial tears medication costs, and other expenses. The distribution of the average direct medical cost component data can be seen in Table 2.

Based on Table 2, the average total direct medical cost for sodium hyaluronate therapy was IDR 386,698 $\pm$ 11,048, higher than the carboxymethylcellulose therapy at IDR 298,263 $\pm$ 14,699. The results of the independent t-test show a statistically significant difference between the

two groups ($p = 0.001 < 0.05$), indicating that the use of sodium hyaluronate requires higher direct medical costs compared to carboxymethylcellulose. The largest difference is seen in the cost of medication (artificial tears), which is IDR 144,283 $\pm$ 16,454 in the sodium hyaluronate group and IDR 56,275 $\pm$ 13,836 in the carboxymethylcellulose group. The results of the independent t-test show a p-value of $0.001 < 0.05$, meaning there is a statistically significant difference in medication costs between the two groups. This indicates that the use of sodium hyaluronate requires significantly higher medication costs compared to carboxymethylcellulose. From a pharmacoeconomic perspective, the cost of medication is influenced by the unit price of the product, frequency of use, duration of therapy, and formulation of the preparation.

Sodium hyaluronate is a natural polymer with viscoelastic, mucoadhesive properties, and a better ability to retain water, thereby enhancing the stability of the tear film and accelerating the repair of the ocular surface. These characteristics result in the production process and the price of sodium hyaluronate products generally being higher compared to carboxymethylcellulose (21). The results of the study are consistent with the theory in pharmacoeconomics that direct medical costs

encompass all expenses directly incurred for healthcare services, including medication costs, examination fees, consultation fees, and medical procedures. If all components of care other than medication are relatively the same, then the difference in total costs will be greatly influenced by the price of the therapy used. The sodium hyaluronate group has higher total costs because the drug costs more, not because other medical services cost more.

Table 2. Comparison of Mean Direct Medical Costs

Direct medical costs	Sodium hyaluronate	Carboxymethylcellulose	P-value
Administrative and physician fees	IDR 150,000 ± 0	IDR 150,000 ± 0	NA
Slit-lamp examination costs	IDR 50,000 ± 0	IDR 50,000 ± 0	NA
Medication costs (artificial tears)	IDR 144,283 ± 16,454	IDR 56,275 ± 13,836	0.001*
Other costs	IDR 42,415 ± 10,736	IDR 41,988 ± 6,484	0.764*
Total	IDR 386,698 ± 11,048	IDR 298,263 ± 14,699	0.001*

*independent t-test

Tabel 3. Cost-Effectiveness Analysis

Parameter	ACER SH (IDR)	ACER CMC (IDR)	Δ Cost	Δ Effectiveness	ICER (IDR)
Symptom-free days (days)	37.800	37.236	88.435	2,22 days	39.835/days
DEQ-5 score (points)	57.716	54.230	88.435	1,2 poin	73.696/poin
Schirmer test (mm)	128.900	119.305	88.435	0,5 mm	176.870/mm

Based on the Schirmer test parameters, the average increase was 3.0 mm in the SH therapy group and 2.5 mm in the CMC therapy group, resulting in an additional effectiveness of 0.5 mm in the SH group. The difference in the change in Schirmer test values between the two groups also showed a statistically significant difference ($p=0.001 < 0.05$). The analysis results show that SH has higher costs but also higher effectiveness compared to CMC. This condition necessitates the ICER value to determine its economic value.

The Schirmer findings should also be interpreted alongside differences in lubricant formulation and concentration. Ouyang et al. found that higher hyaluronic acid concentrations improved corneal staining compared with lower concentrations, but did not show a significant advantage in Schirmer testing, tear-film breakup time, or symptom scores [17]. Thus, a higher concentration alone cannot be assumed to

produce better results across all outcomes. Semp et al. identified substantial variation in formulations, diagnostic criteria, disease severity, and follow-up across artificial-tear trials [18]. These differences limit direct extrapolation from other studies to the present 14-day postoperative comparison.

In Table 3. Based on symptom-free days, the ACER value for the SH therapy group is Rp 37,800 per day, while the ACER value for the CMC therapy group is Rp 37,236 per day. The cost difference of Rp 88,435 with an additional 2.22 days results in an ICER value of Rp 39,835 per additional symptom-free day. Based on the DEQ-5 score, the ACER value for the SH therapy group was Rp 57,716 per point, while the CMC therapy group was Rp 54,230 per point. The ICER value was Rp 73,696 per additional one-point improvement in the DEQ-5 score. Based on the change in Schirmer test

values, the ACER value for the SH therapy group was Rp 128,900 per mm, while the CMC group was Rp 119,305 per mm. The obtained ICER value was Rp 176,870 per additional 1 mm increase in the Schirmer test value. The ACER value represents the average cost required to obtain one unit increase in the Schirmer test value.

Descriptively, carboxymethylcellulose has a lower ACER value, making it appear more efficient when only considering the cost-to-effectiveness ratio. However, ACER has limitations because it does not take into account the differences in cost and effectiveness between interventions. Therefore, when two therapies are compared directly, ICER is a more appropriate parameter to use as a basis for decision-making (Savitri and Hanif, 2024).

Based on Table 4, a sensitivity analysis was conducted to assess the extent to which changes in the cost and effectiveness of sodium hyaluronate (SH) and carboxymethylcellulose (CMC) therapy affect the ICER results based on the effectiveness parameter of the Schirmer test. This analysis is important because the results of pharmacoeconomic analysis are not only influenced by the baseline values of cost and effectiveness but also by the uncertainty in the parameters used. CHEERS 2022 recommends reporting uncertainty and the factors that influence economic results [14]. Li et al. highlighted the importance of explicitly reporting the methods, ranges, and rationale used to vary parameters in one-way sensitivity analysis [19]. Accordingly, interpretation of the scenarios requires attention to the selected input ranges; the analysis does not assign probabilities to those scenarios.

Tabel 4. Sensitivity Analysis

Scenario		Cost or Effectiveness	ICER	Difference ICER	Difference ICER (%)
<i>Base Case</i>		IDR 176.870			
SH Cost	Lowest	IDR 366.000	IDR 135.474	-IDR 44.396	-25%
	Highest	IDR 412.000	IDR 227.474	+IDR 50.604	+29%
CMC Cost	Lowest	IDR 282.200	IDR 208.996	+IDR 32.126	+18%
	Highest	IDR 325.500	IDR 122.396	-IDR 54.474	-31%
SH Effectiveness	Lowest	2,1 mm	-IDR 221.087	-IDR 397.957	-225%
	Hiighest	4,0 mm	IDR 58.957	-IDR 117.913	-67%
CMC Effectiveness	Lowest	0,1 mm	IDR 30.495	-IDR 146.375	-83%
	Highest	3,6 mm	-IDR 147.392	-IDR 324.262	-183%

In the base case condition, the ICER value based on the Schirmer test is Rp 176,870. This value indicates that to obtain additional effectiveness of sodium hyaluronate therapy compared to carboxymethylcellulose, an additional cost of Rp 176,870 is required for each additional unit of effectiveness in the Schirmer test (mm). The ICER value serves as a basis for observing changes in outcomes when the cost or effectiveness parameters undergo scenario changes.

The analysis results show that the cost of sodium hyaluronate is one of the parameters that affect the ICER value. When the cost of sodium hyaluronate is reduced to Rp 366,000, the ICER value decreases to Rp

135,474, or changes by -23.40% compared to the base case. Conversely, when the cost of sodium hyaluronate is increased to Rp 412,000, the ICER value increases to Rp 227,474 or changes by +29%. These results are consistent with the basic principle of cost-effectiveness analysis, which states that an increase in intervention costs with relatively unchanged effectiveness will increase the additional cost required to obtain additional effectiveness. Conversely, a decrease in cost will lower the ICER value [13].

Different results are observed in the changes to the carboxymethylcellulose cost scenario. When the cost of carboxymethylcellulose is at its lowest value of Rp

282,200, the ICER value increases to Rp 208,996, with a change of +18%. Conversely, when the cost of carboxymethylcellulose rises to Rp 325,500, the ICER value decreases to Rp 122,396 or -31%. This can occur because carboxymethylcellulose is the comparator therapy. When the cost of the comparator increases, the cost difference between sodium hyaluronate and carboxymethylcellulose becomes smaller, causing the ICER of sodium hyaluronate against carboxymethylcellulose to decrease. Conversely, when the cost of carboxymethylcellulose is lower, the cost difference becomes larger, leading to an increase in the ICER.

In the effectiveness parameter of sodium hyaluronate, variation has a greater impact on ICER compared to cost variation. When the effectiveness of sodium hyaluronate is reduced to 2.1 mm, the ICER value changes to -Rp 221,087, with a relative change of -225% from the base case. Meanwhile, when the effectiveness of sodium hyaluronate increases to 4.0 mm, the ICER value becomes Rp 58,957 or changes by -67%. These results indicate that the ICER is highly sensitive to changes in the effectiveness of sodium hyaluronate. The above results show that the effectiveness of sodium hyaluronate and the effectiveness of carboxymethylcellulose are the parameters most sensitive to changes in ICER, while changes in the cost of sodium hyaluronate and carboxymethylcellulose have relatively smaller effects. This can be seen from the magnitude of the change in ICER when effectiveness is varied compared to when cost is varied. The result is consistent with the concept of cost-effectiveness analysis (CEA), where the ICER value is the ratio between the difference in cost (ΔC) and the difference in effectiveness (ΔE). Since effectiveness is in the denominator of the ICER formula, a small change in ΔE can cause a much larger change in the ICER value compared to changes in the cost component. In the scenarios evaluated here, effectiveness variation had a greater impact; this does not establish that effectiveness uncertainty always exceeds cost uncertainty in economic evaluations. Conventional one-way sensitivity analysis examines the influence of varying one input while holding the others fixed.

Teljeur et al. discussed this interpretation and proposed an alternative approach within probabilistic analysis to assess uncertainty attributable to individual parameters [20]. The present analysis uses conventional scenarios and should not be interpreted as a probabilistic assessment. In the scenario where SH effectiveness falls to 2.1 mm while its cost remains higher, SH is more costly and less effective than CMC; the negative ICER therefore indicates that SH is dominated, rather than economically favourable [13].

Based on the research results, sodium hyaluronate (SH) is a more expensive therapy but provides higher effectiveness compared to carboxymethylcellulose (CMC) in patients with dry eye syndrome post-cataract surgery during a 14-day observation period.

Conclusion

Based on the research results, sodium hyaluronate (SH) is a more expensive therapy but provides higher effectiveness compared to carboxymethylcellulose (CMC) in patients with dry eye syndrome post-cataract surgery during a 14-day observation period.

Materials and Methods

Population and Research subject

The research population consists of all patients who experience dry eye syndrome after undergoing cataract surgery and receiving SH or CMC artificial tears therapy. The research sample includes patients who meet the inclusion criteria and do not meet the exclusion criteria. Inclusion criteria include patients who have undergone cataract surgery, experience dry eye syndrome, receive SH or CMC artificial tears therapy, and are willing to participate in effectiveness measurements during the study period. Exclusion criteria include patients who do not complete the observation period or have incomplete cost or effectiveness data.

Measurement of Effectiveness

Measurement was conducted at the beginning of the study (baseline) and after 14 days of therapy. The DEQ-5 score was obtained using a questionnaire filled out by the patients. The effectiveness value of DEQ-5 was calculated as the difference between the scores before and after therapy.

$$\Delta DEQ5 = DEQ5_{pre} - DEQ5_{post}$$

The Schirmer test was conducted at the beginning and end of the observation period. Positive values indicate an increase in tear production. Changes in Schirmer values are calculated as follows:

$$\Delta Schirmer = Schirmer_{post} - Schirmer_{pre}$$

The number of symptom-free days is calculated based on the number of days during the 14-day observation period when the patient is in a symptom-free condition.

Measurement of Direct Medical Costs

Cost analysis is conducted using the provider's perspective. The cost components calculated are direct medical costs related to the treatment of patients during the study period. The cost components include the cost of artificial tears therapy and medical service components recorded in the administration/finance system of the healthcare facility. The total direct medical costs for each patient are calculated by summing all relevant medical cost components over the 14-day observation period, and then the average is calculated. All costs are expressed in Rupiah (IDR). Cost data is obtained from the finance department and/or healthcare service administration records.

Cost-Effectiveness Analysis

Cost-effectiveness analysis is conducted by comparing the average cost and average effectiveness of SH therapy against CMC. The analysis begins with calculating the Average Cost-Effectiveness Ratio (ACER):

$$ACER = \frac{\bar{x} C}{\bar{x} E}$$

C: average direct medical cost , E: average therapy effectiveness

Next, the Incremental Cost-Effectiveness Ratio (ICER) is calculated if there is a difference in cost and effectiveness between the two therapies:

$$ICER = \frac{\bar{x} C_{SH} - \bar{x} C_{CMC}}{\bar{x} E_{SH} - \bar{x} E_{CMC}}$$

Sensitivity Analysis

Sensitivity analysis is conducted to evaluate the uncertainty of CEA results against changes in cost and effectiveness parameters. One-way sensitivity analysis is conducted by individually changing the main input parameters, then observing the changes in the ICER value. The results of the sensitivity analysis are presented in the form of a tornado diagram to identify the parameters that have the most significant impact on the cost-effectiveness analysis results. Parameters with the largest ICER changes are considered to have the greatest impact on the uncertainty of the research results.

Ethical Clearance

Ethical Approval This research involves human subjects and has obtained ethical approval from the Health Research Ethics Committee of Universitas Muhammadiyah Malang with ethical approval number No.E.5.a/089/KEPKUMM/IV/2026. The research was conducted in accordance with the applicable research ethics principles. All patient data is used for research purposes and its confidentiality is maintained.

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