CyBorD vs. VRD as Induction Therapy in Multiple Myeloma: A Retrospective Study on Kashmiri Patients

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ABSTRACT

Background: Multiple Myeloma (MM) is a clonal plasma cell malignancy that commonly presents with anemia, bone pain, renal dysfunction, and hypercalcemia. While combination regimens like VRD (bortezomib, lenalidomide, dexamethasone) are globally preferred as first-line induction therapy for transplant-eligible patients, real-world data comparing VRD with CyBorD (cyclophosphamide, bortezomib, dexamethasone) remain limited in specific ethnic and resource-constrained settings, including the Kashmiri population.

Objective: To compare the clinical profile, treatment response, and survival outcomes of CyBorD versus VRD as induction regimens in newly diagnosed multiple myeloma patients from Kashmir.

Methods: This retrospective observational study included 101 MM patients treated between January 2015 and June 2022 at a tertiary care center in Kashmir. Patients received either CyBorD (n = 81) or VRD (n = 20). Baseline characteristics, biochemical parameters, response rates, and survival outcomes were analyzed. Kaplan-Meier analysis was used for progression-free survival (PFS) and overall survival (OS).

Results: The median age was 60-years in both groups, with a male predominance. A higher proportion of CyBorD patients presented with ISS Stage III disease (65.4% vs. 40%) and renal dysfunction, reflected by elevated creatinine levels. Lenalidomide, a key component of VRD, was either contraindicated in renal impairment or not freely available during the early study period, influencing treatment selection. The overall response rate (ORR) was comparable between the two regimens (64.3% for CyBorD vs. 68.7% for VRD). The three-year PFS was 67.2% for CyBorD and 60% for VRD. Despite the unequal group sizes, CyBorD showed efficacy even in patients with poor-risk features such as renal impairment.

Conclusion: CyBorD is an effective, accessible, and well-tolerated alternative to VRD in the real-world management of multiple myeloma, especially in patients with renal dysfunction or in settings with limited access to lenalidomide. This study provides valuable regional data and supports the use of CyBorD in resource-constrained environment while highlighting the need for prospective studies with balanced group sizes.

Keywords: MM, VRD, Outcomes, CyBorD, Myeloma.

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INTRODUCTION

Multiple Myeloma (MM) is a hematologic malignancy marked by the uncontrolled proliferation of plasma cells within the bone marrow, leading to various clinical complications such as bone pain, anemia, renal dysfunction, and increased susceptibility to infections. The therapeutic landscape for MM has evolved significantly

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over recent decades, with induction therapy playing a pivotal role in achieving disease control and preparing patients for subsequent treatment like autologous stem cell transplantation (ASCT). Among the induction regimens, two combinations have garnered considerable attention, CyBorD (cyclophosphamide, bortezomib, and dexamethasone) and VRD (bortezomib, lenalidomide, and dexamethasone).

The VRD regimen has been extensively studied in phase III clinical trials, such as the SWOG S0777, which demonstrated that VRD significantly improves progression-free survival (PFS) and overall survival (OS)

compared to lenalidomide and dexamethasone alone. ¹ Based on these findings, VRD is considered the preferred induction regimen for transplant-eligible MM patients in many international guidelines.²

In contrast, the CyBorD regimen, which replaces lenalidomide with cyclophosphamide, has been associated with high response rates and is considered effective, as an alternative, particularly in patients with contraindications to lenalidomide, such as renal impairment, or in regions where access to lenalidomide is limited. The safety profile of both regimens are crucial consideration in treatment selection. VRD has been associated with manageable toxicities, with the most common adverse events being hematologic in nature, such as neutropenia and thrombocytopenia, as well as peripheral neuropathy. The tolerability of VRD makes it a viable option for a broad patient population.

CyBorD is generally well-tolerated, with a safety profile that includes manageable adverse events. The regimen's tolerability has been demonstrated in various studies, making it a viable option, especially in resource-constrained settings.⁵

Despite the global preference for VRD, there is limited data comparing CyBorD and VRD in real-world settings, particularly in specific ethnic groups such as the Kashmiri population. The Kashmir region has a unique demographic and genetic profile, which may influence disease presentation and treatment response. Moreover, access to medications remains a critical factor in treatment decisions, with lenalidomide, an essential component of the VRD regimen, often being less accessible due to cost or availability constraints. Additionally, lenalidomide is not suitable for patients with significant renal impairment, which is a common presentation in this population. In such scenarios, the CyBorD regimens serve as a practical and effective alternative, offering both affordability and suitability for patients with renal dysfunction by using cyclophosphamide, which is more widely available and better tolerated in renal compromise.⁶

This study aims to generate real-world evidence comparing CyBorD and VRD in a tertiary care setting in Kashmir. Given the limited literature on MM treatment outcomes in this population, the findings will help guide clinicians in selecting the most appropriate induction therapy based on efficacy, safety, and feasibility. Understanding the comparative benefits and challenges of these regimens in the Kashmiri population will contribute to more personalized and resource-conscious treatment approaches for multiple myeloma.

METHODOLOGY

This retrospective observational study was conducted at the Department of Clinical Hematology and Bone Marrow Transplant Unit, Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Soura, Srinagar. The study included all patients diagnosed with multiple myeloma based on standard diagnostic criteria and registered at the Regional Cancer Centre (RCC) between January 2015 and June 2022. Patients with smoldering myeloma, monoclonal gammopathy of undetermined significance (MGUS), incomplete investigations, or those who did not receive treatment after diagnosis were excluded.

Data were extracted from RCC medical records, covering the period from patient registration to the follow-up, defined as the date of death, last available medical record, or the end of the study observation period, whichever occurred first. Collected variables included socio-demographic characteristics (age, sex, ethnicity), clinical presentation, laboratory parameters, and comorbidities. Treatment-related data encompassed induction chemotherapy regimens (CyBorD or VRD), treatment duration, and response assessment.

The primary outcomes were overall survival (OS) and progression-free survival (PFS). Time-to-event analyses were performed using Kaplan-Meier survival curves, with OS measured from the date of diagnosis to disease progression or death from any cause. The study was approved by the Institutional Ethics Committee (IEC) of SKIMS, Srinagar (IEC Approval no: SIMS-131/IEC-SKIMS/2022-57). Informed consents were obtained from all the patients before enrollment.

The objective of the study is to assess the efficacy of CyBorD vs. VRD as induction therapies in newly diagnosed multiple myeloma patients, with a focus on response rates and progression-free survival.

Statistical Analysis

Statistical analysis was conducted using SPSS software version 23. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using descriptive statistics such as mean and standard deviation. Kaplan Meier survival analysis was performed to estimate OS and PFS, with log-rank tests used for comparisons between treatment groups. A *p-value* of < 0.05 was considered statistically significant. Median survival times were reported with two-sided 95% confidence intervals.

RESULTS

A total of 101 patients were included in the study, with 81 (80.2%) receiving the CyBorD regimen and 20 (19.8%) receiving the VRD regimen. The median age at presentation was 60 years in both groups, with a slightly wider range in the CyBorD group (34–77 years) compared to the VRD group (45–75 years). The male-to-female ratio was similar between the two regimens, at approximately 2.25:1 for CyBorD and 2.3:1 for VRD.

Presenting Complaints and Performance Status

Generalized weakness was the most common presenting complaint in both groups, observed in 46.9% of CyBorDtreated patients and 45% of VRD-treated patients. Boney pain was more frequently reported in the VRD group (50%) compared to the CyBorD group (27.2%). Azotemia was noted exclusively in the CyBorD group (16.1%), whereas fever was a rare finding in both groups (1.2% in CyBorD, absent in VRD). ECOG performance status at presentation was comparable, with the majority of patients in both groups scoring 1 (51.9% in CyBorD vs. 50% in VRD). However, a slightly higher proportion of VRD-treated patients had an ECOG 0 (10% vs. 1.2% in CyBorD). ECOG 2 was observed in 38.3% of CyBorD patients and 40% of VRD patients, while ECOG 3 was present in 8.6% of CyBorD patients but absent in the VRD group.

Hematological and Biochemical Parameters

The median hemoglobin level was 8.3 g/dL in both groups, but anemia (Hb < 10 g/dL) was more prevalent in CyBorD-treated patients (81.5%) compared to VRDtreated patients (55%). The median total leukocyte count was identical in both groups (5200/ cumm), but a wider range was observed in CyBorD (1400-21500) compared to VRD (2100-10900). Platelet counts were also similar, with a median of 140,000/cumm in both groups. Hypercalcemia was more frequent in CyBorDtreated patients (23.4%) compared to those receiving VRD (10%). Lytic bone lesions were more common in the VRD group (60% vs. 42% in CyBorD). Similarly, elevated lactate dehydrogenase (LDH) levels were more frequently observed in CyBorD-treated patients (29.6%) compared to VRD-treated patients (10%). The median β-2 microglobulin level was significantly higher in CyBorDtreated patients (10,534 mg/dL) than in those receiving VRD (4,705 mg/dL). Conversely, serum albumin levels \geq 3.5 mg/dL were more frequently observed in the VRD

group (55%) compared to CyBorD (40.7%). An albuminto-globulin (A/G) ratio ≥ 1 was noted in 30% of VRD patients and 24.7% of CyBorD patients.

Staging and Myeloma-Defining Events

Myeloma-defining events (MDE) were more common in CyBorD-treated patients (65.4%) compared to VRD-treated patients (45%). According to the International Staging System (ISS), a higher proportion of CyBorD-treated patients were classified as Stage III (65.4%) compared to VRD (40%). Conversely, ISS Stage I was more frequent in VRD-treated patients (25%) than in CyBorD (6.2%). The Revised ISS (R-ISS) classification showed that the majority of patients in both groups were in Stage II (74.1% in CyBorD vs. 75% in VRD). However, Stage III disease was more frequent in CyBorD-treated patients (22.2%) compared to VRD (10%), while Stage I was more prevalent in the VRD group (15% vs. 3.7% in CyBorD).

Treatment Outcomes

The treatment details and outcomes of patients receiving first-line therapy with CyBorD and VRD regimens were analyzed. Supportive therapies, including radiation therapy, zoledronate administration, antiviral prophylaxis, and aspirin usage, varied between the two groups. Radiation therapy was utilized in 21% of patients receiving CyBorD, whereas six patients in the VRD group received this intervention. Zoledronate was initiated at diagnosis in 58% of CyBorD-treated patients compared to 100% in the VRD group. Antiviral prophylaxis was more commonly administered in the CyBorD group (66.7%) than in VRD (100%). Aspirin usage was reported in 22.2% of patients receiving CyBorD, whereas all VRD patients were prescribed aspirin.

Response to Treatment

The overall response rate (ORR), defined as the sum of complete remission (CR) and partial remission (PR) was comparable between the two treatment arms, with 64.3% in CyBorD and 68.7% in VRD. The proportion of patients achieving CR was slightly higher in the CyBorD group (35.7%) compared to VRD (31.2%). However, partial remission was more frequently observed in the VRD-treated group (37.5%) than in the CyBorD group (28.6%). A very good partial response (VGPR) was achieved in 26.8% of CyBorD-treated patients and 31.2% of VRD-treated patients. Stable disease (SD) was observed in 3.6% of CyBorD

patients, while none of the VRD-treated patients had SD. Progressive disease (PD) was recorded in 5.3% of CyBorD patients, whereas no VRD-treated patients exhibited disease progression following upfront therapy.

Survival Outcomes and Follow-up

At the last follow-up, 47 patients (46.5%) were alive, with 33 patients in the CyBorD group and 14 from the VRD group. A total of 23 deaths were recorded in the study cohort, with a higher mortality rate observed in the CyBorD group (n = 20; Progressive disease = 3, Others = 17) compared to the VRD group (n = 3; Progressive disease = 1, Others = 2). Additionally, 31 patients were lost to follow-up, with a significant proportion from the CyBorD group (n = 28), whereas only 3 patients from the VRD group were lost to follow-up.

The three-year OS was comparable between the two regimens, with CyBorD achieving an OS of 82.4% and VRD slightly higher at 83.1%. This suggests that both regimens effectively prolong survival, with a marginal advantage observed in the VRD group. Median OS has not been reached for either group. However, when assessing progression-free survival (PFS), a notable difference was observed. The 3-years PFS for CyBorD-treated patients was 67.2%, which was higher than that observed in the VRD group (60%).

DISCUSSION

Multiple myeloma is a hematological malignancy characterized by the clonal proliferation of plasma cells, resulting in a range of clinical manifestations. While extensive data exist on MM in Western populations, studies focusing on specific ethnic groups, such as the Kashmiri population, remain limited. This discussion aims to compare the clinical characteristics, treatment regimens, and outcomes of MM patients in the Kashmiri cohort with existing data from both Western and Indian studies, with a particular focus on the efficacy of CyBorD versus VRD as frontline therapies.

In our study, the median age at diagnosis was 60-years for both the CyBorD and VRD groups, with a male-to-female ratio of approximately 2.25:1 and 2.3:1, respectively. This aligns with findings from other Indian studies, which report a median age of 55-years and a male predominance (69%). Similarly, a South Indian study observed a mean age of 64 with a male-to-female ratio of 1.3:1. In contrast, Western studies typically report a higher median age at diagnosis, around 66 years, with

a male-to-female ratio of approximately 1.5:1. These differences suggest that MM present at a younger age in the Indian population, including the Kashmiri cohort.^{7,8}

Generalized weakness was the most common presenting complaint in both treatment groups, observed in 46.9% of CyBorD-treated patients and 45% of VRDtreated patients. Bone pain was more frequently reported in the VRD group (50%) compared to the CyBorD group (27.2%). These findings are consistent with other Indian studies, where bone pain and fatigue were predominant symptoms. In Western populations, bone pain is also a common presenting symptom, reported in approximately 68% of patients. The similarity in clinical presentations across different populations underscores the universal nature of MM symptoms.^{8,9} Anemia was more prevalent in the CyBorD group (81.5%) compared to the VRD group (55%). This is higher than the 50% prevalence reported in some Indian studies. Hypercalcemia was observed in 23.4% of CyBorD-treated patients and 10% of VRD-treated patients, which is higher than the 18.8% reported in the South Indian cohort. Lytic bone lesions were more common in the VRD group (60%) compared to the CyBorD group (42%), aligning with the 84% prevalence reported in other Indian studies. Elevated β-2 microglobulin levels, another marker of tumor burden, were also markedly elevated in the CyBorD group (median 10,534 mg/dL) than in the VRD group (4,705 mg/dL), yet the response and survival outcomes remained comparable to VRD.8

A higher proportion of CyBorD-treated patients were classified as ISS Stage III (65.4%) compared to the VRD group (40%). This is consistent with other Indian studies, where a majority of patients presented with advanced-stage disease. In contrast, Western studies often report a more even distribution across ISS stages. The predominance of advanced-stage presentation in the Indian population may be attributed to delayed diagnosis and limited access to healthcare facilities. The higher ISS Stage III prevalence in CyBorD-treated patients (65.4% vs. 40%) further supports the argument that CyBorD can be effective in advanced disease.

In our study, 80.2% of patients received the CyBorD regimen, while 19.8% received the VRD regimen. The overall response rate (ORR) was comparable between the two groups: 64.3% in the CyBorD group and 68.7% in the VRD group. These response rates are consistent with those reported in other studies, where CyBorD demonstrated an ORR of 84%, with 63% achieving VGPR or better.

 Table 1: Baseline characteristics of the study patients.

Characteristics	CyBorD	VRD	Total
Total Patients	81	20	101
Median Age in years, range	60 (34–77)	60 (45–75)	60 (34–77)
Gender, n (%) Male Female M: F	56 (69.1%) 25 (30.9%) 2.24:1	14 (70%) 6 (30%) 2.3:1	70 (69.3%) 31 (30.7%) 2.25:1
Presenting complaints, n (%) Azotemia Bony Pains Fever Generalized Weakness	13 (16.1) 22 (27.2) 1 (1.2) 38 (46.9)	10 (50%) - 9 (45%)	13 (12.9%) 32 (31.7%) 1 (0.9%) 47 (46.5%)
ECOG, n (%) 0 1 2 3	1 (1.2%) 42 (51.9%) 31 (38.3%) 7 (8.6%)	2 (10%) 10 (50%) 8 (40%)	3 (3%) 52 (51.5%) 39 (38.6%) 7 (6.9%)
Hemoglobin (gm/dL), median (range)	8.3 (4.2–15)	8.3 (5.5–14.4)	8.3 (4.2–15)
Anemia (< 10 gm/dL) at presentation, n (%)	66 (81.5%)	11 (55%)	77 (76.2%)
Total Leukocyte Count /cumm, median (range)	5200 (1400–21500)	5200 (2100–10900)	5200 (1400–21500)
Platelet Count x 10 ⁶ /cumm	140000 (13000–386000)	140000 (52000–305000)	140000 (13000–386000)
Hypercalcemia, n (%)	19 (23.4%)	2 (10%)	21 (20.8%)
Lytic lesions, n (%)	34 (42%)	12 (60%)	36 (35.6%)
Elevated LDH, n (%)	24 (29.6%)	2 (10%)	26 (25.7%)
β-2-microglobulin (mg/dL), median (range)	10534 (1909–40804)	4705 (2269–17682)	7975 (1909–40804)
Sr. Albumin (≥ 3.5 mg/dL), n (%)	33 (40.7%)	11 (55%)	44 (43.6%)
A/G (≥ 1) Ratio, n (%)	20 (24.7%)	6 (30%)	26 (25.7%)
Plasma cell (%), median (range)	55 (6–90)	40.5 (2–90)	53.5 (2–90)
M-Spike (%), median (range)	2.8 (0–9.7)	3.7 (0.4–6.9)	3 (0–9.7)
Immunofixation electrophoresis (IFE), n IgA/Kappa IgA/Lambda IgG/Kappa IgG/Lambda IgM/Kappa Kappa Lambda Nil	6 12 22 16 1 5 14	3 1 9 5 - 2	9 13 30 21 1 7 14 6
Myeloma defining event (MDE), n (%)	53 (65.4%)	9 (45%)	62 (61.4%)
ISS Stage, n (%) 1 2 3	5 (6.2%) 23 (28.4%) 53 (65.4%)	5 (25%) 7 (35%) 8 (40%)	10 (9.9%) 30 (29.7%) 61 (60.4%)
R-ISS Stage, n (%) 1 2 3	3 (3.7%) 60 (74.1%) 18 (22.2%)	3 (15%) 15 (75%) 2 (10%)	6 (5.9%) 75 (74.3%) 20 (19.8%)

Table 2: Treatment details and outcomes of the study patients on first-line treatment.

Treatment details	CyBorD (n = 81), n (%)	VRD, n (%)	Total, n (%)
Radiation Therapy	17 (21%)	6	23
Zoledronate on diagnosis	47 (58%)	20	67
Antiviral prophylaxis	54 (66.7%)	20	74
Aspirin usage	18 (22.2%)	18	36
Treatment response post-upfront treatment	(assessed = 56)	(assessed = 16)	(assessed = 72)
 Overall Response Rate (CR+PR) Complete Remission (CR) Partial Remission (PR) Very Good Partial Response (VGPR) Stable Disease (SD) Progressive Disease (PD) 	36 (64.3%) 20 (35.7%) 16 (28.6%) 15 (26.8%) 2 (3.6%) 3 (5.3%)	11 (68.7%) 5 (31.2%) 6 (37.5%) 5 (31.2%)	47 (65.3%) 25 (34.7%) 22 (30.5%) 20 (27.8%) 2 (2.8%) 3 (4.2%)
At Last follow-up Alive Death Lost to follow-up	33 20 28	14 3 3	47 23 31
3-years Overall Survival (OS)	82.4%	83.1%	73.1%
3-years Progression Free Survival (PFS)	67.2%	60%	66.7%

Similarly, VRD has been associated with high response rates in various studies. Our findings suggest that both regimens are effective in the Kashmiri population. ¹⁰ The three-year OS was comparable between the two groups, with CyBorD achieving an OS of 82.4% and VRD slightly higher at 83.1%. Median OS has not been reached for either group due to limited follow-up duration, but early survival trends are promising. This aligns with findings from other studies, where the median OS for the CyBorDtreated patients were 103.8 months, and for VRD-treated patients, it was 101.7 months. The PFS at 3-years was higher in the CyBorD group (67.2%) compared to the VRD group (60%). These survival outcomes are comparable to those reported in Western populations, suggesting that both regimens are effective in prolonging survival among MM patients. 3,5,10,11

In this study, the majority of patients (80.2%) received the CyBorD regimen, while 19.8% received VRD. This skewed distribution reflects the real-world challenges faced during the early phase of the study (2015 – 2018), when lenalidomide was costly and not freely available. As a result, clinicians preferred CyBorD, which was more accessible and affordable.

Moreover, renal dysfunction at presentation, specifically elevated serum creatinine, was observed

exclusively in the CyBorD group (16.1%). This is noteworthy, as lenalidomide is contraindicated in patients with significant renal impairment. Thus, CyBorD remained the only feasible option for such patients. Interestingly, despite this unfavorable prognostic factor, patients in the CyBorD group demonstrated survival outcomes comparable to those in the VRD group. This suggests that CyBorD is highly effective even in patients with poor baseline renal function. Another key limitation that needs acknowledgment is the unequal number of patients in each group (81 vs. 20). This disparity affects the robustness of direct percentage-based comparisons and statistical significance. Nevertheless, the trends observed still provide meaningful clinical insights.

This study is the first to compare CyBorD and VRD as frontline regimens in multiple myeloma patients specifically from the Kashmiri population, addressing a significant gap in regional data. Despite limitations such as its retrospective design, small sample size, and unequal group distribution, the findings suggest that while VRD remains the internationally preferred induction therapy, CyBorD is a practical and effective alternative, particularly in resource-constrained settings or in patients with renal impairment.

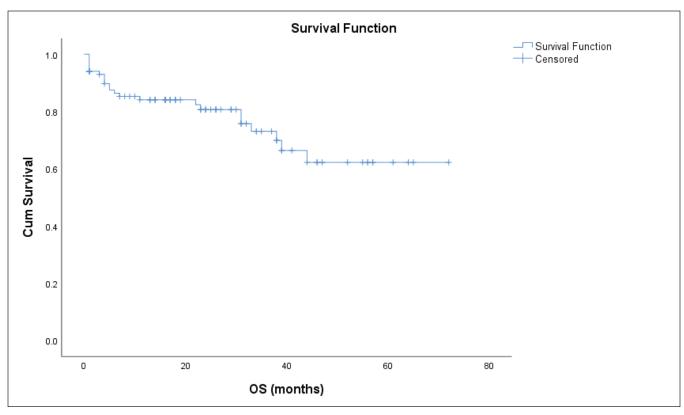


Figure 1: Kaplan-Meier curve depicting the Overall Survival (OS) of the study cohort.

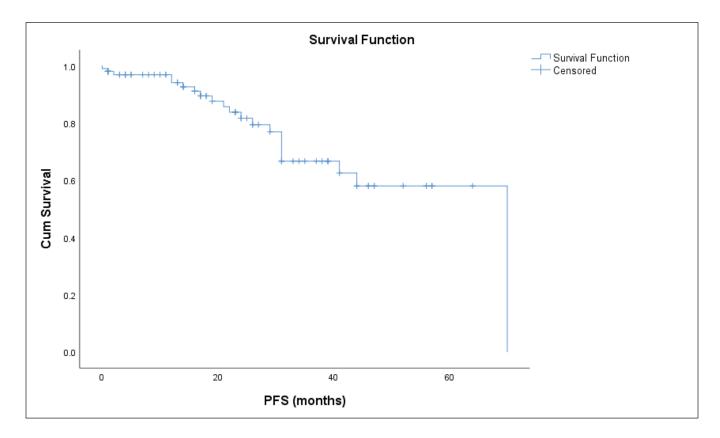


Figure 2: Kaplan-Meier curve depicting the Progression-Free Survival (PFS) of the study cohort.

CONCLUSION

In conclusion, this study provides real-world evidence comparing CyBorD and VRD as upfront therapy for multiple myeloma in the Kashmiri population. Both regimens showed comparable outcomes in terms of response and survival, with VRD showing slightly better tolerability and supportive care adherence, while CyBorD was used more frequently in patients with advanced disease and renal impairment. These findings highlight CyBorD as an effective and accessible alternative to VRD, especially in resource-limited settings or when lenalidomide use is restricted. The study underscores the importance of generating region-specific data to guide personalized treatment decisions and improve outcomes in diverse patient populations.

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