Impact of Antiviral Treatment on Long-Term Prognosis in Non-Immunocompromised Patients With CMV Reactivation

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Research Article

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Abstract

Background. Reactivation of human cytomegalovirus (CMV) occurs in non-immunocompromised patients with or without specific organ involvement, but it is still unknown whether it has a clinical implication on long-term prognosis or not.

Methods. A retrospective cohort study evaluating non-immunocompromised adult patients with CMV reactivation was conducted during the period between January 2010 and February 2018. Patients were divided into ganciclovir-treated and non-treated groups. Patients who died within 30 days from CMV reactivation were excluded as they died from complex causes of conditions. Survivors were followed for 30-months to evaluate long-term prognosis.

Results. A total of 136 patients with CMV reactivation was included, consisting of 66 ganciclovir-treated (48.5%) and 70 non-treated (51.5%) patients. Overall, patients were old-aged (median 70 years old) and most were treated with pneumonia of any cause (91.2%). More patients in ganciclovir-treated group were treated at intensive care unit (43.9% vs 24.3%, respectively) and had higher viral load over 5,000 copies/ml (48.5% vs 22.9%) than non-treated group (all $P < 0.05$). Primary and secondary endpoints including 30-months survival (28.0 vs 38.9%, respectively) and 12-months survival (40.3% vs 49.2%) were not statistically different between the ganciclovir-treated and non-treated groups. In the multivariate analyses, ganciclovir treatment was not associated with 30-months survival (HR 1.307 95% CI 0.759-2.251) and 12-months survival (HR 1.533 95% CI 0.895-2.624).

Conclusion. In a retrospective cohort study evaluating non-immunocompromised patients with CMV reactivation, ganciclovir treatment was not associated with long-term prognosis. Antiviral treatment in this condition would not be necessary unless organ involvement is suspected.

Introduction

Human cytomegalovirus (CMV) is an important viral pathogen in immunocompromised patients, especially those with human immunodeficiency virus (HIV) infection, receiving solid organ transplantation (SOT), or receiving hematopoietic stem cell transplantation (HCST) [1]. Non-immunocompromised patients, broadly defining those without HIV infection or exogenous immune-suppression, had not been considered at-risk populations for CMV diseases. However, growing evidence suggests that CMV reactivation also occurs in non-immunocompromised patients with severe illness and would be associated with higher mortality and prolonged hospitalization [2–10]. CMV reactivation in these hosts could be an indicator of severe illness rather than a determinant. However, it has been suggested that CMV infection may cause chronic inflammation and potentially associated with adverse outcomes such as cardiovascular events [11]. It is still unclear whether CMV reactivation would cause chronic inflammation and has adverse effects on long term prognosis. Because the clinical significance of CMV reactivation is unknown, treatment with patients with CMV reactivation has not been determined. Therefore, the impact of antiviral treatment for CMV reactivation on long term clinical outcome in non-

immunocompromised patients is also unknown [5, 7, 12]. Ganciclovir, an antiviral agent, is the available treatment for CMV infection only in immunocompromised patients. However, we administered ganciclovir to several critically ill, non-immunocompromised patients with CMV reactivation. Therefore, we compared whether the long-term prognosis differ by antiviral treatment in non-immunocompromised patients with CMV reactivation.

Methods

Patients

This is a retrospective cohort study of patients with CMV reactivation at Konkuk University Hospital, a 850-bed, community-based tertiary medical center in Seoul, Republic of Korea between January 2010 and February 2018. Patients were tested for CMV real time polymerase chain reaction (RT-PCR) based on the clinical judgement of the attending physician. CMV reactivation was defined as CMV DNAemia (> 270 copies/ml) in blood by RT-PCR. Patients with hematologic or oncological disorders, with HIV infection, or with previous history of pathologically confirmed CMV disease, or those who had received solid organ transplantation or those who discontinued ganciclovir within 3 days or received other antiviral agents were excluded. Patients who died within 30 days were excluded from the analysis (Fig. 1).

Clinical data collection

Data were collected from hospital database including the administrative, pharmaceutical, and laboratory information at Konkuk university Hospital. Clinical records were reviewed, including treatment with ganciclovir, age, sex, the presence of underlying disease, intensive care unit (ICU) stay, length of hospital stay after CMV reactivation, mechanical ventilation, pneumonia, and maximum titer of CMV PCR. The severity of underlying disease at the time of CMV reactivation was estimated using Charlson's weighted index of comorbidity (CWIs). The severity of illness at the time of CMV reactivation was assessed using quick sequential organ failure assessment (qSOFA) score. The primary endpoint was the 30-months survival. The secondary endpoints were 90 days survival rand 1 year survival.

CMV PCR assays

The Real-Q CMV DNA quantification kit (Real-Q assay; BioSewoom, Seoul, Korea) was used for detection of CMV DNA in blood. The kit is designed to detect CMV genome in purified DNA samples via the gene coding for the glycoprotein B (gB) and allows for fast and reliable assessment of CM-viral loads from various samples, including whole blood, plasma, serum, or urine, using real-time PCR [13]. Results are indicated in copies per milliliter of plasma (copies/ml).

Statistical analysis

The baseline characteristics were compared between the groups of patients treated and not treated antiviral agent using Mann-Whitney U test for continuous variables and Fisher's exact tests for categorical variables. We used Cox proportional hazard regression analysis to evaluate the association

between antiviral treatment and long termprognosis. In the multivariate-adjusted model, we included ICU stays (yes/no), qSOFA score, CWIs, age, CMV PCR titer more than 5,000 copies/ml (yes/no), and variables with statistical significance in the univariate analysis were included in the multivariate analysis. For all analyses, a two-tailed *p* value < 0.05 was considered statistically significant. IBM SPSS Statistics version 25.0 for Windows (IBM, Armonk, NY, USA) was used for all statistical analyses. The present study was approved by Institutional review board (IRB) of Konkuk university of medical center. Informed consent was waived by the IRB of Konkuk university of medical center since the electronic medical record was reviewed retrospectively with de-personalized identification number

Results

Patients characteristics

A total of 737 patients were positive of CMV PCR in blood, of which 136 adult patients with CMV reactivation were finally included in the study cohort (Fig. 1). Demographic characteristics of the patients between ganciclovir treated group and non-ganciclovir treated group are shown in Table 1. 66 patients were treated with ganciclovir (48.5%). There were no significant differences between the ganciclovir treated group and non-ganciclovir treated group with regard to age, sex, mechanical ventilation, qSOFA and CWIs. The proportion of patients who stayed in ICU (43.9% vs. 24.3%, P = 0.015) and who had > 30 days of hospitalization (63.6% vs 44.3%, P = 0.024) were higher in the ganciclovir treated group compared to the non-treated group (Table 1). The number of patient with CMV PCR titer over 5,000 copies/ml is higher in ganciclovir-treated group than non-treated group (48.5% vs 22.9%, P = 0.002).

Table 1
Baseline characteristics of patients between ganciclovir treated group and non-ganciclovir treated group

Variables	Ganciclovir treated (n = 66)	Ganciclovir non-treated (n = 70)	P value
Sex, male	47 (71.2)	40 (57.1)	0.088
Age (years)	71.5 (62.25-80)	69 (59.75-76)	0.419
Pneumonia	60 (90.9)	64 (91.4)	0.915
Severity variables			
ICU	29 (43.9)	17 (24.3)	0.015
Mechanical ventilation	16 (24.2)	10 (14.3)	0.140
Quick SOFA	1 (0–2)	1 (1–1)	0.650
CWI	1 (1–2)	1 (0-1.25)	0.177
Hospital days > 30 days after CMV positive	42 (63.6)	31 (44.3)	0.024
CMV PCR titer > 5,000	32(48.5)	16 (22.9)	< 0.002
CMV positive duration	12 (9–19)	8.5 (7-15.5)	0.137
Progress to CMV pneumonitis	10 (15.2)	0 (0)	0.001
Endpoint			
30 months survival-rate	14/50 (28)	21/54 (38.9)	0.240
1 years survival-rate	25/62 (40.3)	30/61 (49.2)	0.323
90 days survival rate	47/63 (74.6)	60/69 (87)	0.070
Cardiovascular event	4 (6.1)	2 (2.9)	0.363
Data are expressed as number (%) of patients or median (IQR)			
Abbreviations : ICU, intesive care unit; SOFA, sequential organ failure assessment ; CWI, Charlson's weighted index of comorbidity; CMV, Cytomegalovirus ; PCR, polymerase chain reaction			

Long term prognosis in patients with CMV reactivation

In the univariable analysis, no variables were positively associated with 30-months survival. In the multivariable analysis, qSOFA score (HR 1.472; 95% CI 1.001–2.163, P = 0.049) were significantly associated with 30-months survival. Ganciclovir treatment was not associated with 30-months survival (HR 1.307; 95% CI 0.759–2.251, P = 0334) (Table 2). The 1-year survival also showed statistically similar

results. In the multivariable analysis, qSOFA score was significantly associated with 1-year survival (HR 1.595; 95% CI 1.049–2.426, P = 0.029). Ganciclovir treatment was not associated with 1-year (Table S1) and 90 days survival (Table S2).

Table 2
Association between baseline characteristics of patients and 30-months survival

	Univariate		**Multivariate**	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex	1.231 (0.739–2.050)	0.425		
Age	0.985 (0.970–1.001)	0.062	0.987 (0.971–1.004)	0.132
Ganciclovir treated	1.175 (0.727–1.898)	0.511	1.307 (0.759–2.251)	0.334
Pneumonia	1.353 (0.543–3.369)	0.516		
ICU	0.943 (0.566–1.570)	0.821	0.656 (0.354–1.213)	0.179
Mechanical ventilation	1.367 (0.779-2.400)	0.276		
Quick SOFA	1.326 (0.935–1.880)	0.113	1.472 (1.001–2.163)	0.049
CWI	0.884 (0.689–1.135)	0.335	0.904 (0.699–1.168)	0.796
Hospital days > 30	0.893 (0.553–1.442)	0.644		
CMV PCR titer > 50,000	1.094 (0.648–1.848)	0.736	0.926 (0.519–1.654)	0.796
Progress to CMV disease	0.377 (0.092–1.541)	0.175		
Cardiovascular event	1.276 (0.312–5.221)	0.734		

Abbreviations : ICU, intesive care unit; SOFA, sequential organ failure assessment ; CWI, Charlson's weighted index of comorbidity; CMV, Cytomegalovirus ; PCR, polymerase chain reaction

Discussion

There was no statistically significant association between ganciclovir treatment and long term prognosis in the multivariate analysis. As far as we know, this is the first study to compare long-term prognosisbetween ganciclovir treated group and non-ganciclovir treated group in non-immunocompromised patients with CMV reactivation. There are several studies on the association between CMV reactivation and poor prognosis such as mortality, longer hospitalization and mechanical ventilation among critically ill immunocompetent patients [4–6, 10, 14–16]. Although the direct adverse effects of CMV infection on various organs have been suggested [10, 17], clinical significance of CMV reactivation based solely on blood CMV titers is still unknown. In addition, whether CMV reactivation is associated with increased risk of death or whether it is simply another marker of critically ill status

including impairment of cell-mediated immunity is still controversial [5, 7, 12]. Because the meaning of CMV reactivation is unknown, treatment with patients with CMV reactivation has not been determined. Therefore, there are is no clinical guideline on when to administer antiviral agent for CMV reactivation in non-immunocompromised patients. This study could be one of the evidence suggesting that treatment of CMV reactivation in non-immunocompromised patients may not be necessary.

Patients who died within 30 days after CMV reactivation were excluded from the study because patients with severe state are more likely to receive ganciclovir and could show higher mortality rate. Despite excluding patients who died within 30 days after CMV reactivation, patients who stayed in ICU or hospitalized more than 30 days definitely received more ganciclovir treatment. Ten out of 66 patients who treated with ganciclovir probably progressed to CMV pneumonitis which showed broncho-alveloar lavage (BAL) or sputum CMV PCR over 10,000 copies/ml. On the other hand, no patient out of 70 patients who were not received ganciclovir progressed to CMV pneumonitis. CMV PCR titer was significantly higher in the ganciclovir treated group. Even if there is insufficient evidence of ganciclovir treatment in non-immunocompromised patients, it would be the result reflecting the efforts of the physicians to try anything to critically ill patients. However, there was no statistically significant association between ganciclovir treatment and 30-months survival in the multivariate analysis. The result of this study that qSOFA scores correlate with CMV reactivation is the same result as studies confirming CMV reactivation found in critically ill patients [6, 7, 16].CMV as a potential risk factor for the development of cardiovascular disease has been the suggested by means of several epidemiologic, clinical, and laboratory studies [11, 18]. Therefore, we also assessed the development of cardiovascular events according to ganciclovir treatment in study patients. Four patients out of 136 patients developed cardiovascular event, but there were no statistically differences between ganciclovir treated group and non-ganciclovir treated group. (6.1% vs 2.9%, P = 0.363)

In the present study, we includes patients with chronic obstructive pulmonary disease, interstitial lung disease, or connective tissue diseases. As a result, long-term or high-dose steroid users were also included. Strictly speaking, it could be difficult to say them non-immunocompromised. It was thought that patients with these underlying diseases were equally distributed in the ganciclovir treated group and non-ganciclovir treated group, so it would not have a significant effect on the study results.

Our study has several limitations. First, it was a retrospective study, it is subject to confounding by indication. Treatment of ganciclovir were not randomized and was likely to be provided to patients with higher severity and higher risk of mortality. Systematic monitoring of CMV PCR titer was not performed and nearly half of patients had lost follow up within 30 months after discharge. Second, there is a potential selection bias because the test for CMV PCR was performed in a selective group of patients. Third, this study was based on patients at a single center and the results may not be generalizable to other population. Fourth, the side effects of drug in ganciclovir treated group could not be assessed. Finally, we do not know the serologic status of included patients. The prevalence of CMV-specific antibody varies in the worldwide, and seroprevalence in the Korean population has been reported to be relatively high. Although there are no nation-wide surveillance data in Korea, some studies targeted

special group such as pregnancy and solid organ transplantation have reported 96–98% CMV IgG seroprevalence. Because we could assume that most patients in this study were CMV seropositive, we did not collect data on CMV-specific antibody results [19, 20].

In conclusion, our study showed that ganciclovir treatment of CMV reactivation in non-immunocompromised patients did not improve long termprognosis. Further randomized controlled trials are needed to evaluate the clinical impact of antiviral agents effect on CMV reactivation in non-immunocompromised patients.

Abbreviations

CMV
Cytomegalovirus ; HIV:human immunodeficiency virus ; SOT:solid organ transplantation ; HSCT:hematopoietic stem cell transplantation ; RT-PCR:Reverse-transcriptase polymerase chain reaction ; ICU:intensive care unit ; CWIs:Charlson's weighted index of comorbidity ; qSOFA:quick sequential organ failure assessment

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Konkuk university of medical center. The study was performed in accordance with the guidelines followed as per the Declaration of Helsinki. Informed consent was waived since the electronic medical record was reviewed retrospectively with de-personalized identification number

Consent for publication

Consent for publication and sharing our data was obtained in association with consent to participate

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

All authors declare that they have no competing interest.

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Authors' contributions

Conceptualization: J.-H.K.,G.E.P.; investigation: G.E.P.; laboratory work and methodology : G.E.P; supervision: G.E.P.; writing–review and editing: J.-H.K., H.K.K., G.E.P. All authors have read and agreed to the publication of this manuscript.

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Not applicable

References

1. Gandhi MK, Khanna R: **Human cytomegalovirus: clinical aspects, immune regulation, and emerging treatments**. *Lancet Infect Dis* 2004, **4**(12):725–738.
2. von Muller L, Klemm A, Weiss M, Schneider M, Suger-Wiedeck H, Durmus N, Hampl W, Mertens T: **Active cytomegalovirus infection in patients with septic shock**. *Emerging infectious diseases* 2006, **12**(10):1517–1522.
3. Chiche L, Forel JM, Roch A, Guervilly C, Pauly V, Allardet-Servent J, Gainnier M, Zandotti C, Papazian L: **Active cytomegalovirus infection is common in mechanically ventilated medical intensive care unit patients**. *Critical care medicine* 2009, **37**(6):1850–1857.
4. Osawa R, Singh N: **Cytomegalovirus infection in critically ill patients: a systematic review**. *Critical care (London, England)* 2009, **13**(3):R68.
5. Jaber S, Chanques G, Borry J, Souche B, Verdier R, Perrigault PF, Eledjam JJ: **Cytomegalovirus infection in critically ill patients: associated factors and consequences**. *Chest* 2005, **127**(1):233–241.
6. Ong DS, Spitoni C, Klein Klouwenberg PM, Verduyn Lunel FM, Frencken JF, Schultz MJ, van der Poll T, Kesecioglu J, Bonten MJ, Cremer OL: **Cytomegalovirus reactivation and mortality in patients with acute respiratory distress syndrome**. *Intensive care medicine* 2016, **42**(3):333–341.
7. Limaye AP, Kirby KA, Rubenfeld GD, Leisenring WM, Bulger EM, Neff MJ, Gibran NS, Huang ML, Santo Hayes TK, Corey L *et al*: **Cytomegalovirus reactivation in critically ill immunocompetent patients**. *Jama* 2008, **300**(4):413–422.
8. Papazian L, Hraiech S, Lehingue S, Roch A, Chiche L, Wiramus S, Forel JM: **Cytomegalovirus reactivation in ICU patients**. *Intensive care medicine* 2016, **42**(1):28–37.
9. Heininger A, Jahn G, Engel C, Notheisen T, Unertl K, Hamprecht K: **Human cytomegalovirus infections in nonimmunosuppressed critically ill patients**. *Critical care medicine* 2001, **29**(3):541–547.
10. Rafailidis PI, Mourtzoukou EG, Varbobitis IC, Falagas ME: **Severe cytomegalovirus infection in apparently immunocompetent patients: a systematic review**. *Virology journal* 2008, **5**:47.
11. Cheng J, Ke Q, Jin Z, Wang H, Kocher O, Morgan JP, Zhang J, Crumpacker CS: **Cytomegalovirus infection causes an increase of arterial blood pressure**. *PLoS pathogens* 2009, **5**(5):e1000427.
12. Forel J-M, Martin-Loeches I, Luyt C-E: **Treating HSV and CMV reactivations in critically ill patients who are not immunocompromised: pro**. *Intensive care medicine* 2014, **40**(12):1945–1949.

13. Park JE, Kim JY, Yun SA, Lee MK, Huh HJ, Kim JW, Ki CS: **Performance Evaluation of the Real-Q Cytomegalovirus (CMV) Quantification Kit Using Two Real-Time PCR Systems for Quantifying CMV DNA in Whole Blood**. *Annals of laboratory medicine* 2016, **36**(6):603–606.
14. Eddleston M, Peacock S, Juniper M, Warrell DA: **Severe cytomegalovirus infection in immunocompetent patients**. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 1997, **24**(1):52–56.
15. Ziemann M, Sedemund-Adib B, Reiland P, Schmucker P, Hennig H: **Increased mortality in long-term intensive care patients with active cytomegalovirus infection**. *Critical care medicine* 2008, **36**(12):3145–3150.
16. Heininger A, Haeberle H, Fischer I, Beck R, Riessen R, Rohde F, Meisner C, Jahn G, Koenigsrainer A, Unertl K *et al*: **Cytomegalovirus reactivation and associated outcome of critically ill patients with severe sepsis**. *Critical care (London, England)* 2011, **15**(2):R77.
17. Jain M, Duggal S, Chugh TD: **Cytomegalovirus infection in non-immunosuppressed critically ill patients**. *Journal of infection in developing countries* 2011, **5**(8):571–579.
18. Smieja M, Gnarpe J, Lonn E, Gnarpe H, Olsson G, Yi Q, Dzavik V, McQueen M, Yusuf S: **Multiple infections and subsequent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study**. *Circulation* 2003, **107**(2):251–257.
19. Ko JH, Peck KR, Lee WJ, Lee JY, Cho SY, Ha YE, Kang CI, Chung DR, Kim YH, Lee NY *et al*: **Clinical presentation and risk factors for cytomegalovirus colitis in immunocompetent adult patients**. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2015, **60**(6):e20-26.
20. Seo S, Cho Y, Park J: **Serologic screening of pregnant Korean women for primary human cytomegalovirus infection using IgG avidity test**. *The Korean journal of laboratory medicine* 2009, **29**(6):557–562.

Figures

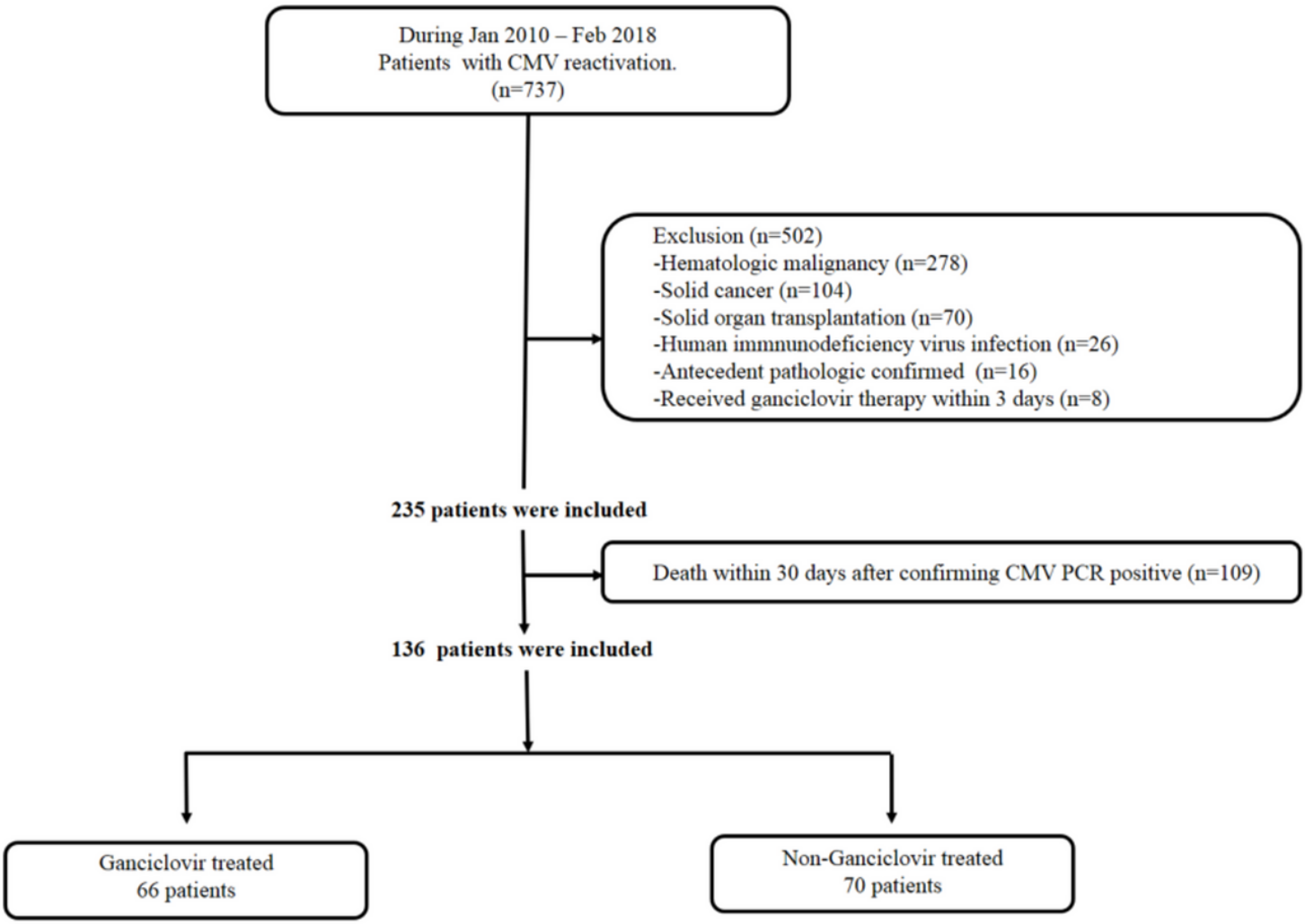

Figure 1

Flowchart of study population among patients with CMV reactivationv

Supplementary Files

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