Research Article

Clinical epidemiology of acute hepatitis C in South America[†]

Short Title: **Acute hepatitis C in South America**

Melisa Dirchwolf [(1)*]; Sebastián Marciano [(2)]; Ezequiel Mauro [(2)]; Andrés Ruf [(3)]; Lucrecia Rezzonico [(4)]; Margarita Anders [(5)]; Daniela Chiodi [(6)]; Néstor Gill Petta [(7)]; Silvia Borzi [(8)]; Federico Tanno[(9)]; Ezequiel Ridruejo[(10)]; Fernando Barreyro[(11)]; Carolina Shulman[(12)]; Pablo Plaza[(13)]; Rodolfo Carbonetti[(14)]; Luciana Tadey[(15)]; Teresa Schroder[(1)]; Hugo Fainboim[(1)]

(1) Hepatopatías Infecciosas, Hospital F.J. Muñiz, Buenos Aires, C1282. Argentina.
(2) Liver Unit, Hospital Italiano de Buenos Aires, C1181. Argentina.
(3) Fundación para la Docencia e Investigación de las Enfermedades del Hígado (FUNDIEH). Buenos Aires, C1426. Argentina.
(4) Hepatología. Hospital de la Asociación Médica Dr. Felipe Glasman, Bahía Blanca, Buenos Aires, 8000. Argentina.
(5) Unidad de Hepatología y Trasplante Hepático, Hospital Alemán, Buenos Aires, C1118. Argentina.
(6) Hospital de Clínicas, Facultad de Medicina, UDELAR, Montevideo, 11600. Uruguay.
(7) Servicio de Gastroenterología y Hepatología, Hospital Central del Instituto de Previsión Social de Asunción, 1209.Paraguay.
(8) Sección Hepatología, HIGA Prof. Dr. Rodolfo Rossi, La Plata Buenos Aires, 1900. Argentina.
(9) Servicio de Hepatología y Gastroenterología. Hospital Provincial del Centenario de Rosario, 2000. Argentina.
(10) Sección Hepatología, Centro de Educación Médica e Investigaciones Clínicas Norberto Quirno "CEMIC".
Unidad de Hepatología y Trasplante Hepático, Hospital Universitario Austral, Buenos Aires, C1431. Argentina.
(11) Laboratorio de Microbiología, Facultad de Química y Ciencias Naturales Universidad de Misiones, Posadas, 3300. Argentina.
(12) Hepatología. Hospital Tornú, Buenos Aires, C1427. Argentina.
(13) Gastroenterología y Hepatología. Salta capital, 4400. Argentina.
(14) Gastroenterología y Hepatología, Hospital de Clínicas Nicolás Avellaneda, Tucumán, 4000. Argentina.
(15) Unidad de Virología, Hospital F.J. Muñiz, Buenos Aires, C1282. Argentina.

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***Corresponding author:** Melisa Dirchwolf

Hepatopatías Infecciosas, Hospital Francisco J. Muñiz.

Tel: +54 362 4904431 Fax: +54 11 49590200 Int: 5370

Address: Uspallata 2272 - CP:1282 - Ciudad Autónoma de Buenos Aires, Argentina.

Email: **mdirchwolf@outlook.com**

Abstract

Backgrounds: There is scarce data pertaining to acute hepatitis C (aHC) infection in South America.

Objectives: To describe clinical characteristics and evolution of aHC in a South American cohort.

Methods: A retrospective survey was conducted at 13 hepatology units. All patients ≥16 years old with aHC diagnosis were included. Demographic, clinical and outcome information were registered in a standardized *ad hoc* questionnaire.

Results: Sixty-four patients were included. The majority were middle-aged (median age: 46 years) and female (65.6%); most of them were symptomatic at diagnosis (79.6%). HCV-1 was the most prevalent genotype (69.2%). Five patients had liver failure: three cases of severe acute hepatitis, one case of fulminant hepatitis and one case of acute-on-chronic liver failure. Nosocomial exposure was the most prevalent risk factor. Evolution was assessed in 46 patients. In the untreated cohort, spontaneous resolution occurred in 45.8% and was associated with higher values of AST/ALT and with the absence of intermittent HCV RNA viremia (p=0.01, p=0.05 and p=0.01, respectively). In the treated cohort, sustained virological response was associated with nosocomial transmission and early treatment initiation (p=0.04 each).

Conclusion: The prevalence of nosocomial transmission in this South-American cohort of aHC stresses the importance of following universal precautions to prevent HCV infection.

Key words: nosocomial transmission; Latin America; epidemiology, hepatitis C virus.

Abbreviations: HCV: hepatitis C virus; aHC: acute infection by hepatitis C; anti-HCV: IgG antibodies for hepatitis C virus; HCV RNA: hepatitis C virus ribonucleic acid; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SVR: sustained virological response; Peg-IFN: pegylated interferon.

Introduction

Hepatitis C virus (HCV) infection has long been considered to be a major public health issue that affects not only developed countries such as the United States (estimated prevalence: 1.3% of the population) and countries in Western Europe (estimated prevalence: 2.4%) but also developing regions such as South America; with an estimated prevalence of 1.2–1.6%[1]. Since HCV progresses to chronic infection in the majority of cases (approximately 75–85%)[2], risk factors for the development of fibrosis, cirrhosis and hepatocellular carcinoma have been the focus of major research efforts. Acute hepatitis C (aHC) represents an entirely different scenario; it is seldom symptomatic (acute hepatitis syndrome occurs in 15% of patients), there is accordingly a considerable paucity of data that precludes precise knowledge of its risk factors and evolution [3].

Acute hepatitis C is defined as an acute necro-inflammatory process of the liver caused by HCV and characterized by an increase in aminotransferases levels of at least 10-fold the upper normal value[4]. It represents a substantial etiology of acute hepatitis; it accounts for approximately 20% of cases of acute hepatitis and approximately 30,000 new cases occur every year in the United States alone[5]. Unfortunately, precise data in developing regions such as South America are scarce. The lack of general data is considered to be multifactorial, a major determinant probably being the elevated number of unrecognized early infections and the insignificant number of acute infections in controlled clinical settings (as were in the past, aHC after blood transfusions)[6].

Accurate identification of patients with aHC and a better understanding of its natural history are important to identifying risk factors for its transmission and selecting the correct timing for antiviral treatment; since it has been suggested that an early start can lead to higher sustained virological response (SVR) rates[7]. The aim of this study was accordingly to identify clinical characteristics and risk factors for aHC in a cohort of South American patients, to analyze factors associated with its

evolution toward chronicity (in an untreated cohort) and the response to antiviral treatment (in a treated cohort).

Materials and methods

Study population: We invited physicians from thirty Gastroenterology and/or Hepatology Units in six South-American countries (Argentina, Uruguay, Brazil, Colombia, Paraguay and Guatemala) to participate in a retrospective survey of aHC. Thirteen units agreed to participate (11 centers in Argentina, one center in Uruguay and one center in Paraguay). Patients with at least 16 years old registered with aHC diagnosis from January 2002 until December 2015 were included; their data was collected using a standardized questionnaire. The aHC diagnosis was based on seroconversion to anti-HCV antibodies (preferred criteria) and/or the presence of an acute hepatitis syndrome (an increase in aminotransferases of at least 10 times the ULN) after the exclusion of other infectious (acute hepatitis A and B), metabolic or toxic etiologies, accompanied by the presence of HCV RNA in the first serum sample (alternative criteria). The study protocol was evaluated and approved by a Clinical Research Committee; this research was conducted in accordance with the Declaration of Helsinki.

Exclusion criteria: An alternative diagnosis for acute hepatitis or concomitant severe illness that precluded an exclusive aHC diagnosis (e.g., systemic cytomegalovirus infection, severe sepsis).

Demographic, possible transmission routes and clinical data: The following data were collected:

1. Demographic data: gender, age at diagnosis.
2. History of exposure to possible risk factors: previous exposure within 6 months before the diagnosis of aHC was recorded (if available in the medical records). The variables that we considered were nosocomial (medically invasive procedures, surgical interventions, transfusions and hemodialysis), occupational (needle-stick injuries or other types of exposure

common in healthcare workers), exposure related to alternative medical procedures (e.g., ozone therapy), sexual (divided accordingly if the patient had a known sero-discordant anti-HCV-positive sexual partner or if the patient had unsafe sex without knowledge of their partner's HCV status) or intravenous drug use. If the patient did not recognize a possible risk factor, he or she was catalogued as having unknown risk exposure.

3. Date of onset (symptomatic patients) or first consult when referred for abnormal liver test (asymptomatic patients).

Serological and molecular HCV RNA assays: Anti-HCV serology was performed using commercially available, third-generation enzyme immunoassays. When available before the diagnosis of aHC, the result and date of testing were recorded. During the episode of aHC, several features regarding anti-HCV were documented: the date of testing compared with the onset of symptoms/first consultation and the number of serological tests performed and their results. We also noted whether seroconversion was confirmed. In terms of molecular HCV RNA testing, both qualitative and quantitative polymerase chain reaction (PCR) testing were performed according to the available technology; when available, we recorded HCV genotype and viral load.

Biochemical features: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin values were registered at aHC onset, and if available, at monthly intervals during the next three months. We also recorded the worst prothrombin time during each aHC episode.

Follow-up and evolution: If patients did not complete at least five months of medical assessment, they were recorded as being lost to follow up; in the remaining cases, patients were sorted according to the decision of the antiviral treatment. In those patients that were not treated, the rate and timing of

spontaneous resolution or evolution toward chronicity were registered. In the cohort of patients that were treated, we recorded the treatment duration, selected drugs and SVR.

Statistical analysis: The results are presented as percentages, mean and standard deviations for normally distributed data and as medians and interquartile ranges for non-normally distributed data. We performed bivariate analysis using the chi-squared or Fisher's test according to the number of patients analyzed for the nominal data, the Student's *t*-test or ANOVA for parametric data and the Mann-Whitney or Kruskal-Wallis test for non-parametric data depending on the number of groups evaluated. We performed multivariate analysis by logistic regression. Statistical analysis was performed using STATA version 11. For all of our analysis, we set the significance level at $p \leq 0.05$.

Results

Demographic and clinical features: Over the course of the study period, 64 patients fulfilled the inclusion criteria. We list the baseline demographic and clinical characteristics of the patients in *Table 1*; the possible sources of infection/risk factors are listed in *Table 2*. The majority of patients were middle-aged and females. The mean age of patients who reported a nosocomial/alternative medical procedure as possible HCV transmission source was 51±13 years, significantly higher than in patients who reported a sexual, occupational, transfusion or drug-related transmission source (42±7, 40±8, 38±16 and 34±2 years respectively; p=0.02). Most patients were symptomatic at diagnosis (79.6%); being the most frequent complaint jaundice. The remaining 13 asymptomatic patients were diagnosed due to altered liver function test results detected during hospitalization or regular check-ups. In 57 patients (89%), ALT and/or AST were elevated ≥10 times the ULN; in the remaining 7 patients, their AST values were 6±2.5 times ULN, and their ALT values were 6±2 times ULN.

- HIV co-infected patients: A total of 8 patients were HIV positive. The median CD4 count, which was available for 6 patients, was 492 (IQR: 180–849) cell/L.

- Disease severity: Five patients exhibited liver failure due to aHC: three patients presented severe acute hepatitis; one patient experienced fulminant evolution requiring liver transplantation one week after aHC onset (with later severe cholestatic HCV recurrence) and finally, one patient with non-alcoholic steatohepatitis-related cirrhosis developed acute-on-chronic liver failure and required a liver transplant 96 hours after aHC episode onset.

The majority of aHC episodes were detected during or after the year 2010 (n=46). When we temporally analyzed the likely source of HCV transmission according to aHC onset, nosocomial and sexually related transmission were the most prevalent risk factors before the year 2010 (33.3% for each risk factor), followed by transfusions (16.7%), unknown (11.1%) and occupational-related transmission

(5.6%). During the period 2010–2015, nosocomial transmission accounted for 50% of the declared risk factors, followed by unknown (19.6%), sexual (13%), intravenous drug use (6.5%), occupational and alternative medical procedures (4.35% for each risk factor) and blood transfusion-related exposure (2.2%).

Serologic diagnosis

Prior HCV serology and seroconversion: Prior negative anti-HCV serology was available in 25 (39%) patients, 18 of whom belonged to high-risk groups for HCV infection (healthcare workers, sexual workers, HIV-positive patients, patients with multiple hospital admissions, hemodialysis and/or a known HCV-positive sexual partner).

Seroconversion yielded an aHC diagnosis in 27 patients (42.1%), occurring with a median of 20 (IQR 3–36) days after the onset of symptoms in the whole group. In 9 patients, the first anti-HCV obtained after consultation was negative, with a median time of 7 (IQR 3.5–23.0) days since the onset of symptoms or the date of an abnormal liver test; these patients presented a positive anti-HCV upon second testing a median of 59 (IQR 32–134) days later.

Virological diagnosis: In 37 patients, aHC diagnosis was made using HCV RNA detection in the setting of an acute hepatitis syndrome without an alternative etiology. The median time for HCV RNA detection was 17 (IQR 10–29) days from the onset of symptoms.

HCV genotypes and viral kinetics: Genotype distribution (available in 52 patients) was as follows:

- Genotype 1 (n=36; 69.2%); distributed as subtype 1a (n=18), 1b (n=15) and no subtype available (n=3).
- Genotype 2 (n=12; 23.1%); distributed as subtype 2a (n=2), 2c (n=3) and 2a/2c (n=7).
- Genotype 3a (n=4; 7.7%)

- No genotype available for 12 patients.

Viral loads were available in 52 patients. Intermittent HCV RNA negativity (at least one negative HCV RNA assay followed by a positive determination) occurred in 9 (17.3%) patients with a median duration of 3 (IQR 1–3) months after the onset of aHC; wide viremic fluctuations of >1 log were detected in 12 (23%) patients.

Follow-up and evolution: After aHC diagnosis, the median follow-up duration was 12.2 (IQR 5.1–22.2) months. We analyzed aHC evolution in 46 patients; 16 patients did not complete the minimum required follow-up duration of 5 months, and 2 patients were transplanted due to fulminant hepatitis/acute-on-chronic liver failure (as described above). The clinical outcomes of patients who completed ≥5 months of follow up are summarized in *Figure 1*.

Untreated cohort

- **Natural course of aHC:** The first described group included 24 patients who were not treated due to a variety of reasons (mainly patient refusal and contraindications); this group allowed us to analyze the natural course of aHC. The median follow-up time of this group of patients was 19 months; 13 patients evolved to chronic infection, and the remaining 11 patients presented spontaneous resolution. This latter group was divided according to their time to viral clearance. In 8 patients, early resolution (≤6 months from aHC onset) was recorded. In three patients, late resolution (>6 months from aHC onset) was confirmed. All of these patients exhibited at least one positive HCV RNA assay 6 months after the onset of disease, with later spontaneous viral clearance. It is noteworthy that one of these patients was co-infected with HIV without highly active antiviral treatment at the time of aHC; the remaining two patients were initially treated as autoimmune hepatitis with high-dose steroid therapy, and their aHC resolved after steroid suspension.

- **Factors associated with spontaneous resolution of aHC.** We analyzed how demographic (sex, age), clinical (HIV status, symptoms, transmission source, biochemical parameters) and virological characteristics (HCV genotype, viral load, intermittent viremia) correlated with spontaneous resolution of aHC: this results was associated with higher values of AST [median and IQR 36 (26-71) U/L compared to 19 (9-24) UNL in chronic evolution; p=0.01] higher values of ALT [median and IQR 40 (29-72) UNL compared to 20 (14-32) UNL in chronic evolution; p=0.05] and with the absence of intermittent HCV RNA viremia [0 compared to 6 (46.1%) cases in chronic evolution; p=0.01]. None of these parameters were statistically significant in our logistic regression analysis.

Treated cohort

The second group included 22 patients who received antiviral treatment.

- **Antiviral treatment:** Only one patient was treated with pegylated interferon (Peg-IFN) monotherapy; the remaining 21 patients received both Peg-IFN and ribavirin (information regarding the fixed or weight-adjusted dose of ribavirin was not obtained). In all patients, the median treatment duration was 24 weeks. The median follow-up time was 14 months. Time of treatment onset information was available in 21 patients. Ten patients received early treatment (≤4 months since aHC onset), and all patients achieved SVR. The remaining 11 patients initiated antiviral treatment >4 months after aHC onset; SVR was achieved in 63.6% of patients in this cohort.
- **Factors associated with sustained virological response.** We analyzed how demographic (sex, age), clinical (HIV status, symptoms, transmission source, biochemical parameters), virological (HCV genotype, viral load, intermittent viremia) and treatment features (onset, duration) correlated with SVR. Viral clearance was associated with a nosocomial transmission [10

patients (58.8%) with SVR referred this risk factor compared to 0 patients in the non-SVR group; p=0.04] and with an earlier onset of antiviral treatment [median and IQR 4 (3-6) months in the SVR group compared to 6.5 (6-7.5) months in the non-SVR group; p=0.04]. None of these parameters were statistically significant in our logistic regression analysis.

Discussion

Because of scant information on the epidemiologic and clinic characteristics of acute HCV patients in South America, we conducted a retrospective survey and performed a multi-study case series analysis of such patients from Argentina, Uruguay and Paraguay.

Although the ages of our patients were similar to those reported in other aHC series [8-10], 44% of our patients (28 individuals) were 50 years or older at the time of infection. This rather high proportion of older patients may be related to the predominance of a nosocomial transmission source; it has been previously suggested that this risk factor prevails in older subjects (>50 years of age)[8]; patients reporting sexual- or drug use-related exposure were significantly younger. The small percentage of patients who declared drug use as a risk factor is concordant with previous reports; intravenous drug addiction related to HCV acquisition has been traditionally considered infrequent in South America [11]. Furthermore, in a prospectively design aHC study conducted in Rio de Janeiro, Brazil, the age and gender distribution were very similar to those of our study population [12].

The most prevalent suspected transmission source was nosocomial, which accounted for 45.3% of cases. The most frequently reported risk factors were programmed surgical procedure/interventions, followed by upper and/or lower endoscopy, multiple hospital admissions or prolonged hospitalizations. These reports were made by the majority of participating centers in recent years (2010–2015), underlying the fact that nosocomial aHC is a current issue, and these are not just colorful statistics from the past. Both in developed and developing countries, nosocomial transmission of aHC has been

extensively reported, particularly since the incidence of HCV infection due to blood product transfusions and intravenous drug use has decreased[13]. In a recent study conducted in Germany, medical procedures were the primary suspected source of infection[5]; similarly, in a Spanish retrospective analysis of 131 patients, 40% of patients reported a non-transfusion related nosocomial source of infection[8]. In a prior South American survey conducted in Brazil, the main risk factors for HCV transmission in aHC patients were related to hospital procedures or admission[14]. The reuse of syringes/needles and the inappropriate use of medication vials in multiple patients have been identified as one of the predominant transmission mechanisms in nosocomial settings[15, 16].

HCV transmission in HIV positive men who have sex with men is broadly recognized[17]; but the risk associated to heterosexual intercourse in HIV negative serodiscordant partners is somewhat controversial (and has even been suggested to be insignificant)[18]. Several studies have reported that sexual contact with a known HCV carrier is a likely source of transmission --especially when moderate-high-risk sexual practices were declared[19-21]. In this survey, only 2 out of 12 patients who acknowledge a sexual contact/risky behavior were HIV positive. Information regarding specific sexual practices or household status of these sexual partners was not obtained—the latter also representing a possible transmission route to consider[22].

We established an aHC diagnosis using the seroconversion criteria in fewer than half of the studied patients (42%); it is important to highlight that the first anti-HCV testing was negative in nine cases despite the presence of symptoms or an altered liver test; seroconversion was only detected in a subsequent analysis performed a median of 59 days after the onset of disease. In terms of HCV RNA detection, intermittent HCV RNA negativity was observed in 9 patients, and wide viremic fluctuations were noted in 12 patients. These serological and virological dynamics have been extensively described[13, 23-25], reflecting the importance of repeating the determinations of both anti-HCV and HCV RNA not only in a diagnostic algorithm (to avoid false negative testing) but also during follow up since

a patient with a single negative HCV RNA may be categorized as recovered when in fact his or her disease might have evolved to a chronic infection[26].

Although aHC is typically described as an asymptomatic infection[26], the majority of aHC series refer to symptomatic patients who seek medical care, thus enabling a timely identification of the disease. In our cohort, 80% of patients were symptomatic at diagnosis, and 71% developed jaundice during the episode. All patients presented with aminotransferase elevations at least 5-fold higher than ULN, and nearly 90% of patients exhibited ALT and ASL levels 10-fold higher than ULN; these findings are consistent with what has been described in other series of symptomatic aHC patients[6]. Paradoxically, the presence of symptoms has been traditionally welcomed by physicians because features such as jaundice and flu-like symptoms have been reported to be associated with spontaneous resolution [5, 27]. Although the presence of symptoms at diagnosis did not reached statistical significance for viral clearance in this study cohort, we measured a trend in this direction (p=0.09). The small sample size of our cohort likely influenced these results.

Despite the fact that a severe/fulminant evolution associated with aHC is considered to be rare (except when occurring as a superinfection in HBV carriers[4]), we have detected five cases with associated liver failure; two cases even required liver transplantation. Due to the small size of our cohort, however, we were unable to identify factors associated with disease severity. Even so, it should be noted that this evolution is perhaps not as infrequent in South America and should be considered in the severe acute hepatitis diagnostic algorithm.

Deciding whom and when to treat has always been a subject of concern with aHC patients[13, 26]. Spontaneous resolution was observed in 46% of our untreated patients; this evolution occurred within the first four months of onset of disease for the majority of them. Despite the fact that only three patients presented spontaneous viral clearance six months after diagnosis (all three cases were associated with some degree of immune system depression), this late resolution is worth noting since it

demonstrates the difficulties associated with assessing aHC evolution despite close monitoring[28]. These results are consistent with previous reports and major guidelines recommendations that establish that the majority of patients with detectable HCV RNA six months after diagnosis will develop a chronic infection; only 11% of patients who remain viremic at this point will spontaneously clear their infection at some latter time[29-31]. When assessing factors related to evolution, the presence of intermittent HCV RNA viremia was associated with chronicity; elevated surrogate markers of necro-inflammatory activity correlated with spontaneous viral clearance (ALT and AST levels). Noteworthy, this association between aminotransferase levels and spontaneous resolution had been observed previously in an HIV-infected cohort [25].

Regarding the evolution of the treated cohort, patients who received antiviral treatment within the first four months of disease onset exhibited an SVR rate of 100%. The patients treated after this period only demonstrated an SVR of 64%. In our bivariate analysis, we found that both the time of treatment and a nosocomial transmission source were significantly correlated with SVR. There has been some controversy regarding the utility of early treatment initiation; a large prospective study that treated patients 12 weeks after an aHC diagnosis did not report lower SVR rates that those that had been reported previously with earlier treatment (4 weeks after diagnosis)[5, 32]. In a recent study published by Hullegie et al. that discussed the rationale for the timing of treatment initiation in aHC, the authors noted that several major scientific societies have advocated for treatment in the chronic phase of the disease to avoid Peg-IFN regimens and instead use direct-acting antivirals. However, in regions where insurance coverage may only pay for these drugs in those patients that demonstrate an urgent medical need for HCV treatment (such as advanced fibrosis/cirrhosis), Peg-IFN may still be the most effective and only available option for aHC treatment in the short-term future[3].

We note several limitations of our study. Due to its retrospective design, it was impossible to determine beyond "reasonable doubt" the source of an aHC infection; however, participating physicians were

strongly encouraged to only consider a likely transmission route if the risky exposure occurred within six months of the onset of the disease and other possibilities were ruled out. Also, since the survey was conducted exclusively among physicians attending at hepatology clinics, the prevalence of certain risky exposures may be biased—intravenous drug users who do not seek medical attention or incarcerated patients are not represented. Regarding evolution assessment, due to the possibility of intermittent HCV RNA viremia during early infection, patients reported to have resolved aHC may in fact have progressed to chronic infection—as clearly stated previously, when discussing three patients who had spontaneous late resolution.

In conclusion, in this large cohort of South-American aHC the majority of patients had a symptomatic presentation. The most prevalent suspected transmission source was a nosocomial origin, which highlights the importance of following universal precautions to prevent HCV transmission. A severe evolution, although infrequent, was observed in five patients. Spontaneous resolution was associated with ALT/AST levels and the absence of intermittent HCV viremia; SVR was associated with nosocomial transmission and the initiation of early treatment. In settings in which direct-acting antiviral therapy is scarce, early Peg-IFN-based treatment may still play a role in aHC treatment.

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Table 1. **Baseline demographic and clinical characteristics of patients with acute hepatitis C (n=64)**

Variables	**Total n=64**
Age at onset (years) -median and IQR.	46 (40-57)
Gender (female) - no. (%)	42 (65.6%)
HIV positive - no. (%)	8 (12.5%)
Symptomatic at diagnosis - no. (%)	51 (79.6%)
AST* (times per ULN) -median and IQR	23 (12.5-36.5)
ALT* (times per ULN) -median and IQR	29 (17-48)
Total bilirubin* (mg/dL) -median and IQR	7 (1.1-11)
Severe acute hepatitis- no. (%)	3 (4.7%)
Fulminant hepatitis - no. (%)	1 (1.6%)
Acute-on-chronic liver failure- no. (%)	1 (1.6%)

* the highest registered value

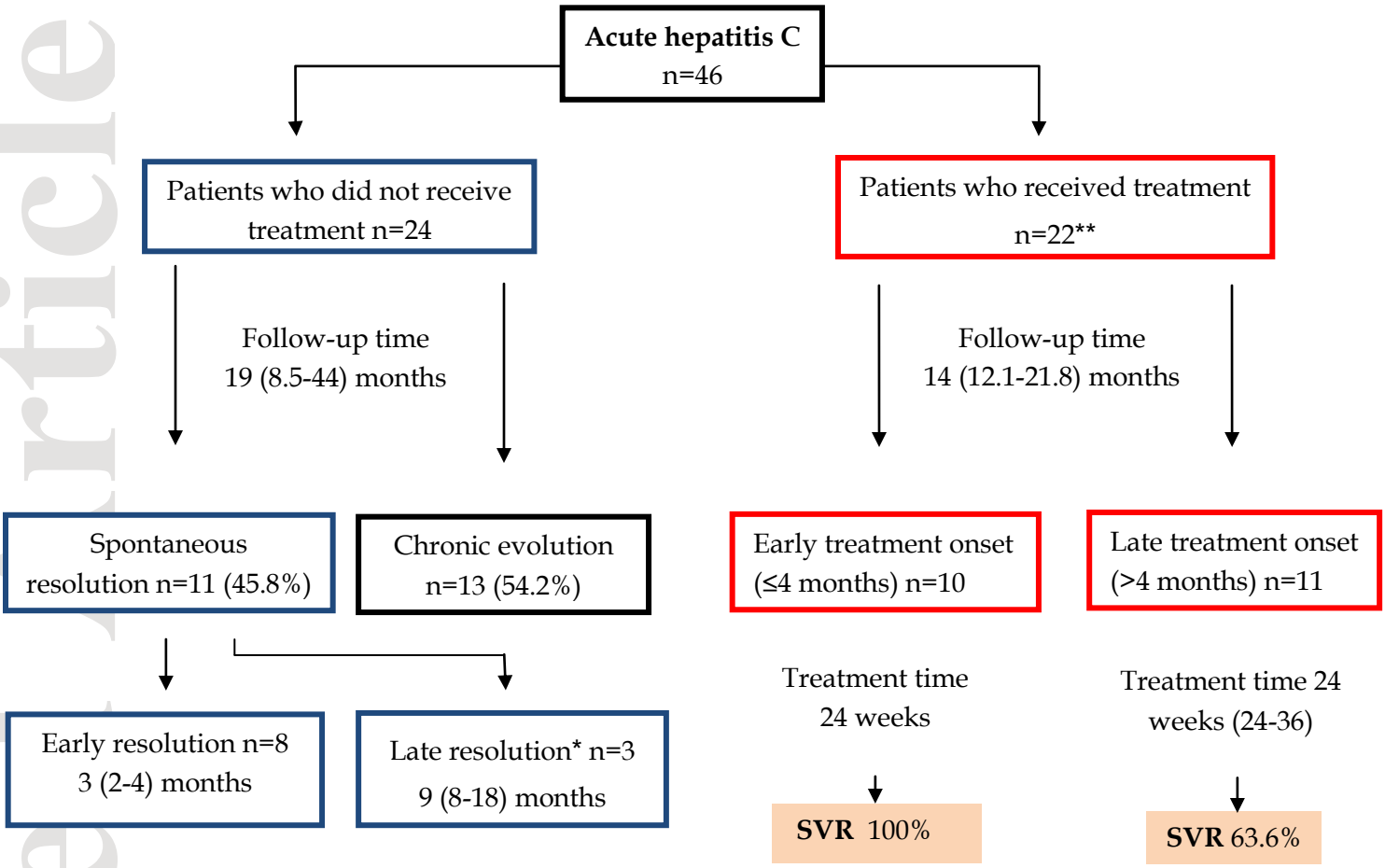
Table 2. **Prevalence of reported risk factors for HCV transmission**

Likely source of HCV infection	**Number of patients (n=64)**
Nosocomial - no. (%)	**29 (45.3%)**
Scheduled surgical procedures/ interventions* - no.	8
Upper and/or lower endoscopy - no.	8
Multiple hospital admissions/ prolonged hospital stay - no.	6
Short hospital admission with parenteral drug administration - no.	2
Hospital admission due to respiratory infection and bronchoalveolar lavage - no.	4
Hemodialysis - no.	1
Blood product transfusion- no. (%)	**4 (6.2%)**
Alternative medical procedures- no. (%)	**2 (3.1%)**
Ozone therapy- no.	2
Occupational exposure- no. (%)	**3 (4.7%)**
Needles stick injury among health-care workers- no.	3
Sexual related exposure- no. (%)	**n=12 (18.8%)**

Known HCV sexual partner- no.	9
Unsafe sexual practices/sexual worker- no.	3
Drug use related exposure- no. (%)	**3 (4.7%)**
Intravenous/Inhalation drug users- no.	3
More than one possible source of infection- no. (%)	**3 (4.7%)**
Unknown exposure- no. (%)	**8 (12.5%)**

*surgical procedures such as renal biopsy, tracheal stent placing, cataract surgery, coronary angioplasty, myomectomy and other obstetric surgery.

Figure 1. **Clinical outcome of aHC patients who completed ≥5 months of follow-up**



Note: All results are presented as median and interquartile range. * Refers to patients who had HCV RNA positive 6 months after disease onset and had latter spontaneous resolution. **22 patients received antiviral treatment for aHC; in one case, information regarding time of treatment onset is missing.