SCORING MODELS FOR PREDICTING HEPATOCELLULAR CARCINOMA RISK IN HCV PATIENTS AFTER ANTIVIRAL THERAPY

Oana Irina Gavril[1], Cristina Iordache[2], Magda-Ecaterina Antohe[2], Codrina Ancuța[1], Radu Sebastian Gavril[1]*, Irina Mihaela Esanu[1]

[1] "Grigore T. Popa" University of Medicine and Pharmacy, Faculty of Medicine, Iași, 700115, Romania

[2] "Grigore T. Popa" University of Medicine and Pharmacy, Faculty of Dental Medicine, Iași, 700115, Romania

***** Corresponding author; e-mail: radu.gavril@umfiasi.ro

ABSTRACT

Hepatitis C virus (HCV) infection is a major global health concern, with a significant risk of developing hepatocellular carcinoma (HCC) in infected individuals. The advent of oral antiviral therapy has revolutionized the management of HCV, achieving sustained virologic response (SVR) rates and reducing the risk of HCC. However, some patients still remain at risk for HCC even after successful antiviral treatment. Scoring systems have emerged as valuable tools to predict HCC risk and assist in post-treatment surveillance. This review aims to summarize and evaluate the existing scoring systems developed to assess HCC risk in HCV patients after oral antiviral therapy. We systematically searched relevant databases for published articles. We included studies that focused on the development, validation, and clinical application of scoring models for HCC risk prediction. We identified scoring systems, utilizing different variables such as demographic data, liver function tests, imaging findings, and genetic markers. We discuss the strengths and limitations of each scoring system and compare their predictive accuracy. Furthermore, we explore the potential for combining multiple scoring models to enhance risk stratification. The findings of this review highlight the utility of scoring systems in identifying patients at higher risk of developing HCC despite achieving SVR with oral antiviral therapy. Additionally, we discuss the implications of these scoring systems for clinical practice, risk stratification, and long-term surveillance of HCV patients. In conclusion, scoring systems offer a valuable approach to estimate the risk of HCC in HCV patients post oral antiviral treatment. A better understanding of these scoring models will help clinicians in tailored follow-up strategies and early detection of HCC, ultimately improving patient outcomes. Further research is needed to refine and validate these scoring systems in different populations and to explore their potential inclusion into clinical guidelines.

Keywords: Hepatitis C virus, hepatocellular carcinoma, sustained virologic response.

INTRODUCTION

Hepatocellular Carcinoma (HCC) is the fifth most common form of cancer and ranks second place in terms of neoplasia-related deaths globally. The incidence of HCC progressively increases with age, peaking in the eighth decade of life (White et al., 2017). Hepatic cirrhosis is a risk factor for tumor development, regardless of its etiology (West et al., 2017). One of the most common global risk factors for HCC is liver cirrhosis secondary to infections with either hepatitis C virus (HCV) or hepatitis B virus (HBV). The incidence of HCC shows significant geographic variations, with most cases in

Asia and Africa attributed to HBV, while HCV poses a major risk in Western countries. The annual risk of HCC is approximately 3% in patients with hepatic cirrhosis and active HCV infection (El-Serag, 2011).

Direct-acting antivirals (DAA) therapy revolutionized the treatment of HCV infection, thanks to its high efficacy and excellent safety profile. This allowed the use of oral antiviral therapy even in decompensated liver disease (Baumert et al., 2019). The introduction of DAA agents has improved sustained virologic response (SVR) rates to over 85% in all HCV genotypes and shortened the duration of treatment (Baumert et al., 2019). DAA therapy has demonstrated high efficiency and safety even in special population groups, such as patients with human immunodeficiency virus (HIV) or HBV coinfection, hemodialysis patients, and those with recurrent HCV infection after liver transplantation. SVR reduces the risk of developing HCV-related liver cirrhosis, and regression of hepatic fibrosis has also been demonstrated (Bachofner et al., 2017, Sporea et al., 2017).

MATHERIAL AND METHODS

This review relies on an analysis of specialized literature accessible in databases like PubMed and Google Scholar, including medical terminologies such as: chronic hepatitis C virus, hepatic fibrosis, hepatocellular carcinoma, sustained virologic response.

RESULTS

Recent models have evaluated the risk of HCC in patients with HCV after antiviral treatment (Ioannou et al., 2018). Among patients without hepatic cirrhosis at the time of DAA treatment, the risk of HCC after achieving SVR exists but is very low. However, in patients with established hepatic cirrhosis before DAA treatment, a substantial absolute risk of HCC persists after SVR, although significantly lower compared to untreated patients and those who did not achieve SVR. Current guidelines recommend that patients with hepatic cirrhosis continue HCC surveillance indefinitely after achieving SVR. The risk of HCC varies widely among patients, both with and without hepatic cirrhosis.

Considering the increased efficacy of DAA therapy, most patients diagnosed with HCV-related hepatic cirrhosis have either already been treated, are currently undergoing treatment, or will be virologically cured in the future. Easily applicable methods are needed to assess the occurrence of HCC in patients with hepatic cirrhosis who achieve SVR, as this is one of the most important determinants of the cost-effectiveness of surveillance.

Risk stratification models for HCC have been developed among post-SVR patients using pre-treatment data. However, the time duration since achieving SVR represents a complexity that has not been accounted for yet. In some patients with hepatic cirrhosis, the resolution of hepatic fibrosis and hepatic remodeling after SVR may lead to a decline regarding the risk of HCC in time. However, certain subjects,

especially those with decompensated HCV-related hepatic cirrhosis, may not exhibit fibrosis resolution and a reduction in HCC risk after SVR. As time passes after SVR, the age may increase and may acquire factors that either decrease fibrosis or attenuate the decline in HCC risk after SVR (type 2 diabetes, obesity, alcohol consumption) or even increase the risk of HCC among individuals without hepatic cirrhosis at the time of treatment (Mihalache et al., 2012).

Numerous studies evaluated the risk of HCC occurrence in patients with chronic HCV infection. These studies aimed to determine the risk of HCC in patients with SVR. One of the well-established risk factors for HCC development after SVR in patients with HCV infection is advanced fibrosis or hepatic cirrhosis (Makiyama et al., 2004). HCC rarely occurs within HCV infection in the absence of hepatic cirrhosis. There is also evidence showing that patients with type 2 diabetes have a higher risk of HCC after achieving SVR (Hung et al., 2011). Several other factors (advanced age, male gender, alcohol consumption, elevated gamma-glutamyl transpeptidase [GGT] levels before and after treatment, high pre-treatment liver cytolysis syndrome, elevated alpha fetoprotein [AFP] tumor marker before and after treatment, low pre-treatment and post-treatment albumin levels) have also been associated with HCC occurrence in post-SVR patients (Hiramatsu et al., 2015). Another application of risk stratification for HCC can be used to propose different surveillance tests for different risk categories (Darrick, Raumond, 2015)(tab. I).

Table I.Risk factors for HCC post-SVR in patients with HCV infection

Study	SVR subjects	Follow-up period (years)	Risk factors/scores
Makiama 2004	1197	5.9	Age >50 years Male gender Fibrosis f3/f4
Ikeda 2005	1056	4.7	Age >60 years AST > 100 U/L Platelets <150,000/μL
Chang 2012	871	3.4	Fibrosis f3/f4 Age >60 years AFP >20 ng/ml after treatment Platelets <150,000/μL
Arase 2013	1751	8.1	Diabetes mellitus Male gender

			Alcohol consumption Age (for every 10 years)
Oze 2014	1425	3.3	AFP >5ng/ml after treatment Age >65 years
Yamashita 2014	562	4.8	Fibrosis f2/f3/f4 Age >50 years Alcohol >30g/d AFP >8ng/ml before treatment
Huang 2014	642	4.4	GGT >75 U/L Age >65 years "Fibrosis f2/f3
Toyoda 2015	522	7.2	Diabetes mellitus Fibrosis f4
Chang 2015	801	5.0	Age >60 years AFP >20 ng/ml after treatment Platelets <150,000/l Fibrosis f3/f4

AFP- alpha fetoprotein, AST-aspartate aminotransferase, GGT-gamma-glutamyl transpeptidase, SVR- sustained virologic response

Efficient, expensive, and labor-intensive invasive strategies such as computed tomography (CT) or magnetic resonance imaging (MRI) examinations can be cost-effective if indicated in high-risk groups (Goossens et al., 2017). Although these models have been mentioned in patients with HCV-related hepatic cirrhosis, post-HCV antiviral treatment, and HBV infection, the calculation of HCC risk is still investigated.

In patients with decompensated hepatic cirrhosis who achieved SVR, a reduction in the Model for End-Stage Liver Disease (MELD) score and hepatic venous pressure gradient has been observed (Foster et al., 2016, Lens et al., 2017). Recent data also show that SVR reduces hepatic and overall mortality (Backus et al., 2019). The WHO goal of eradicating HCV infection may reduce the risk of HCC by preventing the progression of HCV-related liver cirrhosis, enabling fibrosis regression, and diminishing

the carcinogenic effect of the virus (Lazarus et al., 2017, Ioannou, Feld, 2019). However, recent studies have shown conflicting data regarding the increased risk of HCC occurrence and recurrence in patients who achieved SVR (Reig et al., 2016, Conti et al., 2016). Additionally, as mentioned before, the financial resources required for expanding services and therapy costs present significant limitations, especially in resource-limited countries (Ward, Hinman, 2019).

Since 2014, the use of DAA has significantly reduced the high number of chronic HCV cases. However, this decline has been countered by a substantial increase in the prevalence of nonalcoholic fatty liver disease (Wong et al., 2014, Gavril et al., 2016). Chronic viral hepatitis C remains the second major cause for liver transplantation in waitlist subjects (Noureddin et al., 2018).

The introduction of DAA treatment has resulted in both short-term and long-term clinical benefits due to achieving SVR (Ioannou et al., 2018). Previous prospective studies using Interferon-based therapy have also shown evident proofs, demonstrating that treatment was strongly associated with a reduced risk of HCC (Bruix et al., 2011).

Morgans meta-analysis evaluated the presumed benefit and demonstrated that achieving SVR with Interferon was associated with a 76% reduction in the risk of HCC (Morgan et al., 2013). However, there are studies which show that SVR induced by DAA did not reduce the prevalence of HCC and even suggest a short-term increased risk of recurrence in patients previously treated for HCC (Reig et al., 2016, Conti et al., 2016). A study (Conti et al., 2016) following 374 cirrhotic patients without HCC, treated with DAA for 24 weeks, reported HCC occurrence in 9 out of 285 patients (3.2%) and HCC recurrence in 17 out of 59 patients (28.8%) previously treated for HCC. Child-Turcotte-Pugh (CTP) class and HCC history were independently associated with HCC development, but neither HCV genotype nor DAA therapeutic regimen correlated with HCC occurrence. Additional reports suggest alarming rates of de novo HCC diagnosis in 6 out of 66 patients (9%) after 6 months of DAA treatment cessation (Reig et al., 2016) and 4 out of 54 patients (7.4%) after a 12-month follow-up (Cardoso et al., 2016). These studies have limitations (single-center, uncontrolled, without long-term follow-up periods), thus excluding well-defined conclusions. In contrast, multiple large cohort studies have demonstrated that DAA-induced SVR is associated with a reduced risk of HCC occurrence (Kanwal et al., 2017, Ioannou et al., 2017, Li et al., 2018). Among 22,500 patients treated with DAA, there were 271 new cases of HCC that occurred after DAA treatment, including 183 patients with SVR (Kanwal et al., 2017). 79 out of 22,579 (0.34%) cases developed HCC during DAA treatment and were excluded from the study. The risk of HCC was higher in those with HCV-related hepatic cirrhosis compared to those without hepatic cirrhosis. SVR was associated with a 76% reduction in the risk of HCC compared to those who did not achieve SVR. Moreover, HCC diagnosed during treatment was not more aggressive compared to those that occurred after treatment.

In a retrospective study, over 60,000 veterans with HCV who received antiviral

therapy between 1999 and 2015, including DAA, Interferon, or combination treatments, were evaluated (Ioannou et al., 2017). Cases of HCC diagnosed within 6 months of treatment initiation were excluded. Patients with SVR after DAA treatment showed a 71% reduction in the risk of HCC compared to cases of DAA treatment failure. Furthermore, the risk reduction of HCC associated with SVR was similar regardless of achieving SVR solely through DAA, solely through Interferon treatment, or through combination therapies, suggesting that HCV eradication reduces the risk of HCC, regardless of the antiviral regimen.

A meta-analysis of 26 observational studies on HCC occurrence highlighted a higher incidence of HCC in patients with DAA-induced SVR compared to Interferon-induced SVR (2.96/100 patients/year and 1.14/100 patients/year). Patients treated with DAA were older and were followed up for a shorter period (Waziry et al., 2017). In another study, DAA therapy was not associated with an increased risk of HCC compared to Interferon. A large cohort study that included 17,836 HCV-infected veterans in the United States compared patients treated with DAA to those treated with Interferon and untreated patients (Li et al., 2018). Patients treated with DAA showed a significantly higher incidence of HCC compared to those treated with Interferon, but the subjects also had a significant rate of known risk factors for HCC, including cirrhosis, older age, and elevated AFP tumor marker levels. A subanalysis of cirrhotic subjects who achieved SVR did not show statistically significant differences in HCC incidence between the groups treated with DAA and Interferon.

Furthermore, untreated cirrhotic subjects had a twofold higher incidence of HCC compared to both treated groups. There was a notable increase in the risk of HCC occurrence by 3.73% per 1000 individuals per year in a cohort of 1123 patients with hepatic cirrhosis treated with DAA during a follow-up period of 19.6 months (Mariño et al., 2019). Consistent with the results in veteran cohorts, the risk was higher in patients without SVR compared to those who achieved SVR, and disease severity (CTP class B, C, high liver stiffness, clinical presence of portal hypertension, hepatic decompensation) also played a role. Moreover, the study (Mariño et al., 2019) highlights an increased risk of HCC (up to three times) in the presence of hepatic nodules before DAA treatment, compared to patients without nodules or with well-defined benign nodules. It appears that the most crucial factor in reducing the risk of HCC is the eradication of HCV, with a similar risk reduction achieved whether through DAA or Interferon therapy. However, a higher number of HCC cases may be observed after DAA therapy, as more patients are treated, and a higher proportion of them are older and have advanced liver diseases (Ioannou et al., 2019). Another controversy is whether there is a higher risk of tumor recurrence in patients with HCC treated with curative intent (either through resection or radiofrequency ablation) after achieving SVR. Unexpectedly high rates of HCC recurrence have been reported in patients with a complete radiologic response after DAA treatment. HCC

recurrence was detected in 17 out of 59 (28.8%) patients in an Italian study and in 16 out of 58 (27.6%) patients in a Spanish population during a six-month follow-up period. However, the small number of patients, lack of a control group of untreated patients, and short follow-up limit any clear conclusions regarding the malignancy potential of anti-HCV treatment and risk factors for recurrence (Reig et al., 2016).

Two large controlled studies highlight that there are no increases in HCC recurrence in patients who were adequately treated for HCC and received DAA compared to untreated individuals (Cheung et al., 2016, Singal et al., 2019). In a clinical study, 314 subjects who underwent liver transplantation for HCC were treated with DAA (Kershaw et al., 2006). The mean time duration between liver transplantation and initiation of DAA treatment was 67 +/- 60 months. HCC recurrence was observed in only seven patients (2.2%). Most of these patients (5/7) presented with predictive factors for recurrence based on histological criteria of the native liver. Moreover, two patients experienced recurrence after liver transplantation, but before the introduction of DAA treatment. Thus, incomplete treatment or misstaging of the tumor initially may lead to misinterpretation in retrospective studies. This can result in a misattribution of DAA as responsible for HCC recurrence.

To further assess the risk of HCC recurrence after DAA compared to the risk after Interferon treatment, meta-analyses and metaregression of studies comparing HCC incidence and recurrence after DAA and Interferon treatment were performed (Waziry et al., 2017, Nagata et al., 2017, Nishibatake et al., 2019). The same meta-analysis and metaregression of studies comparing HCC incidence and recurrence after DAA and Interferon treatment (Waziry et al., 2017) demonstrated no differences in HCC recurrence. Additionally, a Japanese analysis also showed no significant differences in HCC recurrence between patients treated with Interferon or those treated with DAA (Nagata et al., 2017). The cumulative incidence of HCC recurrence in patients who achieved SVR was significantly lower compared to patients without SVR under both forms of treatment. Another Japanese study highlighted recurrence rates after DAA treatment of 39% and 61% at one and two years, respectively, with no significant differences (Nishibatake et al., 2019). Achieving SVR was not significantly associated with the risk of early HCC recurrence in a multivariate analysis, but tumor factors such as a history of multiple HCC treatments or short periods without recurrences were identified as independent risk factors for recurrence after antiviral treatment.

CONCLUSIONS

While oral antiviral therapy has transformed the management of HCV, the risk of HCC remains a critical concern in these patients. Existing HCC risk scoring systems offer valuable guidance, but their applicability to the post-DAA era needs further evaluation. Advancements in risk prediction models and personalized approaches may contribute to improved HCC risk stratification and facilitate timely

interventions for better patient outcomes. Continuous research and collaboration among experts in hepatology and oncology are vital in addressing this evolving clinical challenge.

REFERENCES

1. White DL, Thrift AP, Kanwal F, Davila J, El-Serag HB. Incidence of Hepatocellular Carcinoma in All 50 United States, From 2000 Through 2012. Gastroenterology 2017; 152: 812-820.
2. West J, Card TR, Aithal GP, Fleming KM. Risk of hepatocellular carcinoma among individuals with different aetiologies of cirrhosis: A population-based cohort study. Aliment Pharmacol Ther 2017; 45: 983-990.
3. El-Serag HB. Hepatocellular carcinoma. N Engl J Med 2011; 365: 1118-1127.
4. Baumert TF, Berg T, Lim JK, Nelson DR. Status of Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection and Remaining Challenges. Gastroenterology 2019; 156: 431-445.
5. Bachofner JA, Valli PV, Kröger A et al. Direct antiviral agent treatment of chronic hepatitis C results in rapid regression of transient elastography and fibrosis markers fibrosis-4 score and aspartate aminotransferase-platelet ratio index. Liver Int 2017; 37: 369-376.
6. Sporea I, Lupușoru R, Mare R et al. Dynamics of liver stiffness values by means of transient elastography in patients with HCV liver cirrhosis undergoing interferon free treatment. J Gastrointestin Liver Dis 2017; 26: 145-150.
7. Ioannou GN, Green PK, Berry K. HCV eradication induced by direct-acting antiviral agents reduces the risk of hepatocellular carcinoma. J Hepatol 2018; 68: 25–32.
8. Mihalache L, Graur LI, Popescu DS, Niţă O, Graur M. Anthropometric parameters--predictive factors for cardio-metabolic diseases. Rev Med Chir Soc Med Nat Iasi 2012;116(3):794-798.
9. Makiyama A, Itoh Y, Kasahara A et al. Characteristics of patients with chronic hepatitis C who develop hepatocellular carcinoma after a sustained response to interferon therapy. Cancer 2004; 101: 1616–1622.
10. Hung CH, Lee CM, Wang JH et al. Impact of diabetes mellitus on incidence of hepatocellular carcinoma in chronic hepatitis C patients treated with interferon-based antiviral therapy. Int J Cancer 2011; 128: 2344–2352.
11. Hiramatsu N, Oze T, Takehara T. Suppression of hepatocellular carcinoma development in hepatitis C patients given interferon-based antiviral therapy. Hepatol Res 2015; 45: 152– 161.
12. Darrick KLi, Raumond T. Impact of hepatitis C virus eradication on hepatocellular carcinogenesis. Cancer 2015: 2874-2881.
13. Goossens N, Singal AG, King LY. Cost-effectiveness of risk score-stratified hepatocellular carcinoma screening in patients with cirrhosis. Clin Transl Gastroenterol 2017; 8: 101.
14. Foster GR, Irving WL, Cheung MC et al. Impact of direct acting antiviral therapy in patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016; 64: 1224-1231.

15. Lens S, Alvarado-Tapias E, Marino Z et al. Effects of All-Oral Anti-Viral Therapy on HVPG and Systemic Hemodynamics in Patients With Hepatitis C Virus-Associated Cirrhosis. Gastroenterology 2017;153: 1273-1283.
16. Backus LI, Belperio PS, Shahoumian TA, Mole LA. Impact of Sustained Virologic Response with Direct- Acting Antiviral Treatment on Mortality in Patients with Advanced Liver Disease. Hepatology 2019; 69: 487-497.
17. Lazarus JV, Wiktor S, Colombo M, Thursz M. EASL International Liver Foundation. Micro-elimination - A path to global elimination of hepatitis C. J Hepatol 2017; 67: 665-666.
18. Ward JW, Hinman AR. What Is Needed to Eliminate Hepatitis B Virus and Hepatitis C Virus as GlobalHealth Threats. Gastroenterology 2019; 156: 297-310.
19. Wong RJ, Cheung R, Ahmed A. Nonalcoholic steatohepatitis is the most rapidly growing indication for liver transplantation in patients with hepatocellular carcinoma in the U.S. Hepatology 2014; 59: 2188-2195.
20. Gavril RS, Mitu F, Leon MM, Mihalache L, Arhire LI, Grosu C, Gherasim A, Nita O, Ungureanu IO, Oprescu AC, Graur M. Biomarkers of Inflammation in Patients with Type 2 Diabets Mellitus and Hepatic Steatosis. Rev Chim (Bucharest) 2016;67(9):1828-1831.
21. Noureddin M, Vipani A, Bresee C et al. NASH Leading Cause of Liver Transplant in Women: Updated Analysis of Indications For Liver Transplant and Ethnic and Gender Variances. Am J Gastroenterol 2018; 113: 1649-1659.
22. Bruix J, Poynard T, Colombo M et al. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. Gastroenterology 2011; 140: 1990-1999.
23. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: A meta-analysis of observational studies. AnnIntern Med 2013; 158: 329-337.
24. Reig M, Marino Z, Perello C et al. Unexpected high rate of early tumor recurrence in patients with HCV-related HCC undergoing interferon-free therapy. J Hepatol 2016; 65: 719-726.
25. Conti F, Buonfiglioli F, Scuteri A et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. J Hepatol 2016; 65: 727-733.
26. Cardoso H, Vale AM, Rodrigues S et al. High incidence of hepatocellular carcinoma following successful interferon-free antiviral therapy for hepatitis C associated cirrhosis. J Hepatol 2016; 65: 1070-1071.
27. Kanwal F, Kramer J, Asch SM, Chayanupatkul M, Cao Y, El-Serag HB. Risk of Hepatocellular Cancer in HCV Patients Treated With Direct-Acting Antiviral Agents. Gastroenterology 2017; 153: 996-1005.
28. Li DK, Ren Y, Fierer DS et al. The short-term incidence of hepatocellular carcinoma is not increased after hepatitis C treatment with direct-acting antivirals: An ERCHIVES study. Hepatology 2018; 67: 2244.

29. Waziry R, Hajarizadeh B, Grebely J et al. Hepatocellular carcinoma risk following direct-acting antiviral HCV therapy: A systematic review, meta-analyses, and meta-regression. J Hepatol 2017; 67: 1204-1212.
30. Marino Z, Darnell A, Lens S et al.Time association between hepatitis C therapy and hepatocellular carcinoma emergence in cirrhosis: Relevance of non-characterized nodules. J Hepatol 2019; 70: 874-884.
31. Cheung MCM, Walker AJ, Hudson BE et al. HCV Research UK. Outcomes after successful directacting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. J Hepatol 2016; 65: 741-747.
32. Singal AG, Rich NE, Mehta N, et al. Direct-acting antiviral therapy for hepatitis C virus infection is associated with increased survival in patients with a history of hepatocellular carcinoma. Gastroenterology 2019; 157: 1253-1263.
33. Kershaw EE, Hamm JK, Verhagen LA, Peroni O, Katic M, Flier JS. Adipose triglyceride lipase: function, regulation by insulin, and comparison with adiponutrin. Diabetes. 2006; 55: 148–157.
34. Nishibatake Kinoshita M, Minami T, Tateishi R et al. Impact of direct-acting antivirals on early recurrence of HCV-related HCC: Comparison with interferon-based therapy. J Hepatol 2019; 70: 78-86.